EMA/23630/2020
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Beovu

International non-proprietary name: brolucizumab

Procedure No. EMEA/H/C/004913/II/0010

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

© European Medicines Agency, 2022. Reproduction is authorised provided the source is acknowledged.

Table of contents

1. Background information on the procedure

1.1. Type II Variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Limited submitted to the European Medicines Agency on 26 July 2021 an application for a variation.

The following changes were proposed:

Variation requested		Type	Annexes affected
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of visual impairment due to DME for Beovu; as a consequence, sections 4.1, 4.4, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.0 of the RMP has also been submitted.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/0001/2015 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

Description	Actual Date
Start of procedure	14 Aug 2021
CHMP Rapporteur Assessment Report	08 Oct 2021
PRAC Rapporteur Assessment Report	08 Oct 2021
PRAC Outcome	28 Oct 2021
Request for supplementary information	11 Nov 2021
Submission of responses	21 Dec 2021
Re-start of procedure	27 Dec 2021
CHMP Rapporteur Response Assessment Report	25 Jan 2022
PRAC Rapporteur Response Assessment Report	28 Jan 2022
PRAC members comments	02 Feb 2022
Updated PRAC Rapporteur Response Assessment Report	03 Feb 2022
PRAC Outcome	10 Feb 2022
CHMP members comments	14 Feb 2022
Updated CHMP Rapporteur Response Assessment Report	17 Feb 2022
Opinion	24 Feb 2022

2. Scientific discussion

2.1. Introduction

Diabetic macular edema (DME) is characterised by exudative fluid accumulation in the macula. When the area of swelling involves the center of the macula, the fovea, it leads to clinical impairment of vision.

DME is a frequent manifestation of diabetic retinopathy (DR) and is the major cause of vision loss in patients with DR. Patients can develop DME at any stage during the progression of DR.

The pathophysiological processes begin with chronic hyperglycaemia, and interplay between vascular endothelial growth factor (VEGF) and inflammatory mediators.

Estimates of the prevalence of DME in patients with Type I and Type II DM range between 4.2% and 7.9%, and 1.4% and 12.8%, respectively (Lee et al 2015).

The current treatment options for patients with visual impairment secondary to DME are: intravitreal anti-VEGF (which includes ranibizumab (Lucentis®), aflibercept (Eylea®)), laser photocoagulation, intravitreal corticosteroids, or intravitreal corticosteroid implants.

However, intravitreal anti-VEGF treatments can be a significant burden to patients. Thus, there is a need to develop therapies with a longer effect. Additionally, in the context where the efficacy of an anti-VEGF can reduce over the time and requires a switch to another anti-VEGF together with the fact some patients have a poor treatment effect to available therapies lead a need of additional alternatives therapies.

2.2. Non-clinical aspects

2.2.1. Toxicology

2.2.1.1. Introduction

As part of the initial marketing authorization application for the use of brolucizumab for the nAMD indication, the non-clinical safety of up to 6 mg brolucizumab was established for IVT injection in cynomolgus monkeys in Good Laboratory Practice (GLP)-regulated repeated-dose studies.

All repeat-dose IVT toxicology studies were conducted in cynomolgus monkeys as they are the only species in which brolucizumab is both pharmacologically active and possessing a similar ocular anatomy to humans, providing a relevant and well understood animal model in which toxicity following IVT injection can be assessed. In these studies, animals were dosed unilaterally (to provide an untreated contralateral control) with up to 6 mg brolucizumab/50 microliter (μL) injection volume (maximum formulatable dose) using a dosing interval designed to mimic or exaggerate clinical use. Systemic IV toxicity studies were not conducted with brolucizumab due to the extremely low systemic exposure following IVT administration, the lack of systemic toxicity following repeated unilateral IVT injections of up to 6 mg brolucizumab every 3 or 4 weeks, and the extensive clinical experience with vascular endothelial growth factor inhibitors.

In the context of this type II variation to extend the indication to DME patients, the MAH submits an ePPND study in Cynomolgus monkeys.

2.2.1.2. Reproduction toxicity

To evaluate the potential effects of brolucizumab on pregnancy and parturition, lactational transfer, embryo-fetal development and survival, growth, and postnatal development of offspring, an ePPND toxicity study (no.1670189) was conducted in Cynomolgus monkeys.

In response to a question during the assessment, the Applicant has submitted historical data for animals at the same laboratory, to contextualise the findings. The data are shown below:

Table Summary of facility historical control data for abortion incidence by trimester

Historical control data: Abortions	Incidence	Percentage
1st Trimester	15	8.8
2nd Trimester	6	3.1
3rd Trimester	1	0.5

Data based on 12 studies conducted at the Testing Facility during the period of 2013 to 2021 and consists of 194 control animals.

The historical control still birth rate is 13/194 or 6.7% with a range of 0-19%.

Female cynomolgus monkeys (16/group) received IVT injections of brolucizumab at 0,3 or 6 mg in the right eye once every 4 weeks beginning on Day 20 post-coitum (p.c.) to delivery (total 6 doses on days 20, 48, 76, 104, 132, and 160 p.c.). Four females from each group with surviving infants on Day 28 post-partum (p.p.) received an additional dose on Day 28 p.p. and had blood and milk collected for toxicokinetic evaluations.

Criteria for evaluation included clinical observations, pregnancy monitoring, assessments of body weights and body weight changes, parturition, ophthalmic observations, and clinical pathology evaluations for maternal animals. For infants, clinical observations, assessments of body weights and body weight changes, external and morphological examinations, neurobehavioral test batteries, assessments of grip strength and skeletal development, and clinical pathology evaluations were performed for up to 12 weeks postnatal. On day 92 p.p., all surviving maternal animals were necropsied and subjected to a macroscopic examination of the external features of the carcass, and of the uterus. Surviving infants were necropsied on PND92±1 and subjected to a similar macroscopic examination, with additional recording of organ weights. Blood samples were collected for toxicokinetic, monkey chorionic gonadotropin (maternal animals only), and anti-drug antibody (ADA) analyses. The main results are detailed below.

Animal fate: there was no treatment-related mortality amongst maternal animals; a low-dosed female was euthanized in moribund condition on GD133 due to edema of the legs likely due to pregnancy complications. Infant mortality was observed in all groups; none was attributed to maternal exposure to the test-article.

Table 4.1: Summary of Infant Deaths

Animal Number	Sex	Dose Group	Day	Remarks
P0003-1	F	1	PND 0	Failure to thrive
P0010-1	M	1	PND 1	Failure to thrive
P0015-1	F	1	PND 21	Found dead
P0104-1	F	2	PND 16	Trauma
P0110-1	M	2	PND 10	Failure to thrive
P0113-1	F	2	PND 0	Maternal moribund euthanized GD 133
P0201-1	M	3	PND 0	Stillborn
P0207-1	M	3	PND 18	Failure to thrive, poor milk production by maternal
P0209-1	F	3	PND 0	Stillborn
P0214-1	M	3	PND 0	Found dead

GD = Gestation day; PND = Postnatal day

Pregnancy outcome

Gestation length was within the normal, expected range of 134 to 184 days (Van Esch et al., 2008) for all animals and no treatment-related difference in gestation length was noted.

No test article-related effects on the incidence of abortions, stillbirths, or unscheduled deaths were noted. Pregnancy loss (abortions and stillbirths) occurred in maternal control animals and maternal animals

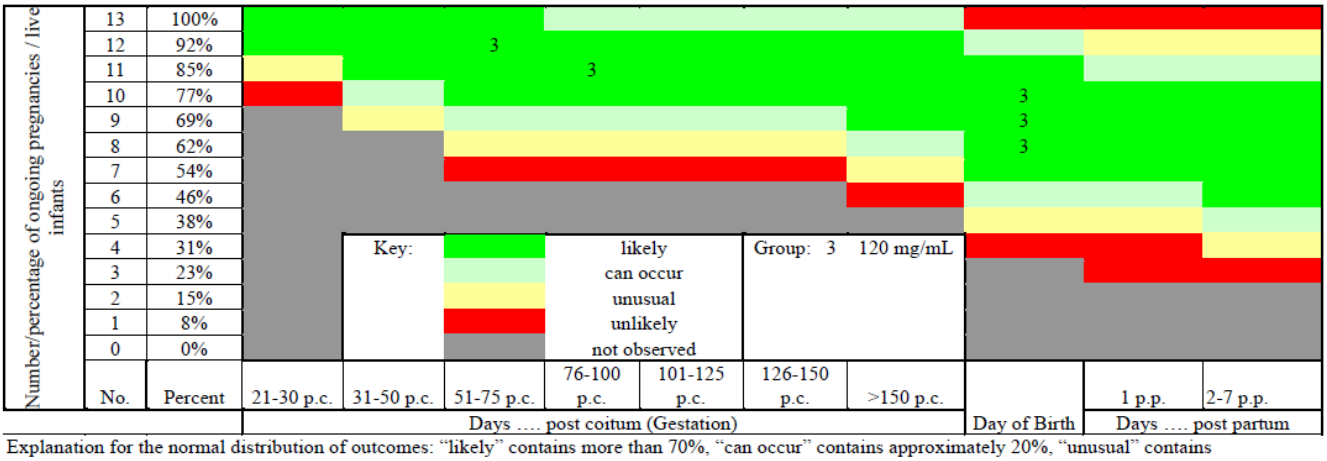
administered 6 mg/eye. Prenatal loss is a common occurrence in this species (Jarvis et al., 2010; Weinbauer et al., 2011a). In the control group, two first-trimester (Days 21 to 50 p.c.) abortions occurred. No pregnancy losses or stillbirths occurred in maternal animals administered 3 mg/eye. In maternal animals administered 6 mg/eye, two second-trimester (Days 51 to 100 p.c.) abortions and two stillbirths occurred. Incidences of abortions and stillbirths were within the normal range, as indicated on the nomogram, and were not attributed to the test article. The total number of surviving infants on PND 7 for each group included 11 from maternal control animals, 14 from maternal animals administered 3 mg/eye, and 8 from maternal animals administered 6 mg/eye.

Table 7.16: Summary of Pregnancy Outcome - Incidence of Abortions, Stillbirths, and Early Infant Deaths

During Gestation	Group 1 0 mg/kg/dose No. (%)	Group 2 50 mg/kg/dose No. (%)	Group 3 100 mg/kg/dose No. (%)
Total number of pregnant females[a]	15[a]	14[a,b]	13[a]
Mean length of gestation (days)	162	165	166
Females with abortion			
1st Trimester Abortions (GD0-50)	2 (13.3%) GD 27, 41	0	0
2nd Trimester Abortions (GD51-100)	0	0	2 (15.4%) GD 65, 83
3rd Trimester Abortions (GD101-144)	0	0	0
Total number of stillbirths (GD144+)	0	0	2 (15.4%) GD 166, 177
Total number of abortions and stillbirths	2 (13.3%)	0	4 (30.8%)
Total number delivered	13 (86.7%)	14 (100%)	9 (69.2%)
Total number of early infant deaths (PND 0-7)	2 (13.3%) PND 0, 1	0[b]	1 (7.7%) PND 0
Total number of infants euthanized or found dead after PND 7	1 (6.7%)[c] PND 21	2 (14.3%)[d,e] PND 10, 16	1 (7.7%)[f] PND 18
Total number of surviving infants to terminal sacrifice	10 (66.7%)	12 (85.7%)	7 (53.8%)

a Maternal animals confirmed not pregnant by monkey chorionic gonadotropin (mCG) analysis were i included in the total number
b Maternal animal P0113 euthanized in moribund condition on GD 133, and fetus, not included in the total number
c Infant P0015-1 found dead on PND 21
d Infant P0104-1 euthanized on PND16 due to injury
e Infant P0110-1 euthanized on PND10 due to failure to thrive
f Infant P0207-1 euthanized on PND18 due to failure to thrive likely due to poor milk production by t maternal

Table 7.20: Nomogram - Group 3



Explanation for the normal distribution of outcomes: "likely" contains more than 70%, "can occur" contains approximately 20%, "unusual" contains approximately 8% and "unlikely" contains approximately 2% of outcomes. Jarvis P, et al. (2010), Weinbauer GF, et al. (2011a) and Weinbauer GF, et al. (2011b)

Clinical observations: no test article-related clinical observations were noted in maternal animals or surviving infants.

Ophthalmic examinations (maternal animals): no test article-related ophthalmic observations were noted in maternal animals. The observations of vitreous cells were noted in all groups (including controls) and were considered due to the dosing procedure.

Body weights: no test article-related alterations in body weight or body weight gain were noted in maternal or infant animals.

External examinations (infants): no test article-related external abnormalities were noted – examinations were performed on PND 1, 7, 14, 21, 28 and then every 4 weeks for up to 3 months.

Morphological examination (infants): no test article-related effect was noted - anogenital distance, left/right arm/leg length, crown-heel length, crown-rump length, eye distance, thorax circumference, tail length were evaluated on PND 1, 21, 56, and 84.

Grip strength (infants): No test article-related effects on infant grip strength on PND 28 were observed. All infants passed this test (ability to hold for at least 30 seconds) or demonstrated the ability to climb.

Neurobehavioural test battery (infants): the data for infants from treated animals were similar to those obtained for infants from the control group. Of note, parameters evaluated on PND 1 and 7 included face color, behaviour in cage, behaviour in hand, respiration rate, observed and elicited postural tones, elicited dorsiflexion, buildup, grasp support, righting reflex, prone progression, clasp support, following of eyes, lipsmack orient, sucking, rooting, snout reflex, pupil response, glabellar tap, nystagmus, and moro reflex.

Skeletal development (infants): radiographic assessments of the entire skeleton conducted on PND50 (±2) did not report any treatment-related pathological finding; skeletal development of infant animals was considered according to age.

Clinical pathology: no treatment-related hematology, coagulation, and clinical chemistry effects were observed in maternal (Days 20 and 132 p.c.) and infant (PND42, 56, 70) animals.

Terminal procedures: no treatment-related effect was noted at macroscopic examination of maternal and infant animals. No test article-related infant organ weight differences were present.

Toxicokinetics

Exposure to brolucizumab in maternal milk or infant serum was not observed after IVT administration of brolucizumab 3 or 6 mg/eye to maternal animals. Serum exposure to brolucizumab in maternal animals increased with the increase in dose level from 3 to 6 mg/eye on Day 48 p.c., Day 132 p.c., and Day 28 p.p. The increases in mean Cmax and AUC_{0-24} values were approximately dose proportional. Exposure was generally similar after multiple monthly doses when compared to the second dose on Day 48 p.c.

Table 2-3 Toxicokinetic Parameters in Maternal Serum

		Brolucizumab Dose (mg/eye)		
Brolucizumab Dose (mg/eye)		0	3	6
Cmax (ng/mL)	Day 48 p.c.	BLQ	224	389
	Day 132 p.c.	BLQ	253	301
	Day 28 p.p.	BLQ	248	483
AUC_{0-24} (ng*h/mL)	Day 48 p.c.	BLQ	3420	6090
	Day 132 p.c.	BLQ	4310	5120
	Day 28 p.p.	BLQ	4820	8100

BLQ = < 5.00 ng/mL for serum

Novartis [Study 1670189]; Covance [Study 8367963]

Anti-drug antibodies (ADA) were detected in some maternal animals and infants. In general, maternal animals screened positive for the presence of ADAs: 8/16 in the control group; 14/16 in Group 2 (3 mg/eye); and 9/16 in Group 3 (6 mg/eye) animals. Infant animals did not screen positive for the presence of ADAs in the control group, but 5/12 in Group 2 (3 mg/eye) infants and 1/7 in Group 3 (6 mg/eye) screened positive for the presence of ADAs. However, no maternal animals showed reduced exposure consistent with an ADA-response, and exposure to brolucizumab was not demonstrated in any infant animal. All infants with anti-brolucizumab antibodies had mothers that were also positive for anti-brolucizumab antibodies but not all mothers positive for anti-brolucizumab antibodies had infants that were positive.

Discussion and conclusion

The rates reported are within the margins of the historical data for animals at the same laboratory. However, the sensitivity of the model is questioned.

During the scientific advice held in February 2016, it was considered that, should an in vivo study be conducted, the intravenous route should be preferably used; the IVT route was challenged since sufficient margin to clinical exposure might not be achieved to allow for firm conclusions. It was also considered that a NOAEL >20-fold higher clinical exposure would provide reassurance regarding a risk to the growing foetus.

In the present study, the IVT route was used and the Cmax-based exposure ratio at the maximal dose of 6 mg/eye was equal to 6. In addition, pre-dosing plasma levels of brolucizumab were not quantifiable (BLQ) in all treated animals on GD48, and in most treated animals on GD132 - 14/15 at 3 mg/eye; 9/11 at 6 mg/eye. This suggests that maternal animals might have been exposed intermittently to the test-article during the treatment period (including organogenesis).

Exposure to brolucizumab in maternal milk or infant serum was not observed in the study. However, brolucizumab may affect placenta (formation, growth) due to its VEGF-inhibiting properties. This point could not be fully addressed in the monkey study since placentas and umbilical cords were collected, but discarded without any evaluation.

Overall, it is not certain that the treatment modalities used in the ePPND study induced sufficient exposure of treated animals to provide reassuring data for human risk assessment. The added value of that study is uncertain since it does not mitigate the known risks of brolucizumab-induced VEGF inhibition for embryo-foetal development.

In response to these concerns, the MAH has amended the SPC 5.3 section to indicate that "based on its pharmacological effect, brolucizumab should be regarded as potentially teratogenic and embryo-foetotoxic".

2.2.2. Ecotoxicity/environmental risk assessment

According to Directive 2001/83/EC and Guideline EMEA/CHMP/SWP/4447/00 corr 2, medicinal products containing vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates, and lipids as an active pharmaceutical ingredient, an ERA should be provided. This ERA may consist of a justification for not submitting ERA studies, e.g. due to their nature they are unlikely to result in a significant risk to the environment.

Brolucizumab is a humanized single-chain Fv (scFv) antibody fragment of vascular endothelial growth factor (VEGF) with a molecular weight of ~26 kDa which inhibits vascular endothelial growth factor A (VEGF-A) binding to its receptors VEGFR1 and VEGFR2. Beovu (brolucizumab) has been approved in the EU on the 13-Feb-2020 for for the treatment of visual impairment related to neovascular age-related macular degeneration (nAMD). The ERA is updated to support the type II variation in which Brolucizumab is being proposed for the treatment of visual impairment related to diabetic macular edema (DME)

Brolucizumab is recombinantly produced in E. coli by standard expression technology and purified by protein refolding and consecutive chromatography steps. The processes are free of any animal-derived or human-derived products.

Brolucizumab is provided as 120 mg/mL solution for injection in a vial and pre-filled syringe and is administered by intravitreal injection.

In addition to the active pharmaceutical ingredient, the drug product contains the following excipients, which are either naturally occurring or not of environmental concern: sodium citrate, citric acid,

polysorbate 80, sucrose, and water for injection. The marketing of Brolucizumab for the indications cited above will not increase the amount of any of these commonly used excipients in the environment to any significant extent.

Any active pharmaceutical ingredient that reaches water streams after use in patients, via eventual spills during Brolucizumab application, or after disposal of an unused drug is expected to be very rapidly degraded by biotic and abiotic processes.

Therefore, to the best of its knowledge, there is no appreciable risk for the environment emerging from the additional use of Brolucizumab for the treatment of diabetic macular edema in the EU market. No further evaluation of Brolucizumab has been provided and this is considered acceptable.

2.2.3. Conclusion on the non-clinical aspects

The added value of the ePPND study is uncertain since maternal animals were not sufficiently exposed to brolucizumab. Therefore, the absence of developmental toxicity observed under the experimental conditions of that study does not mitigate the known risks of brolucizumab-induced VEGF inhibition for human embryo-foetal development. In line with this, a statement in section 5.3 of the SPC has been added as follows: that "based on its pharmacological effect, brolucizumab should be regarded as potentially teratogenic and embryo-foetotoxic".

The applicant provided a suitable justification for not performing an Environmental Risk Assessment (ERA) in line with the guidance from the "Guideline on the Environmental Risk Assessment of the medicinal products for human use" (EMEA/CHMP/SWP/4447/00 corr 2). Brolucizumab is a monoclonal antibody and is unlikely to result in significant risk to the environment. No further evaluation of Brolucizumab has been provided and this was considered acceptable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study no.	Study design, objectives, population	Treatment duration	No. participants Treatment(s)	Efficacy endpoints	Completed/ Ongoing
Non-inferiority studies providing key efficacy data					
B2301 (KESTREL)	Phase III, three-arm, randomized, double-masked, multicenter study assessing the efficacy and safety of brolucizumab versus aflibercept in adult patients with visual impairment due to diabetic macular edema	100 weeks	Total: (N= 566) Brolucizumab 3 mg: 5 x q6w loading then q12w/q8w maintenance (N=190) Brolucizumab 6 mg: 5 x q6w loading then q12w/q8w maintenance (N=189) Aflibercept 2 mg: 5 x q4w loading then q8w maintenance (N=187)	Primary: Change from baseline in BCVA at Week 52 in the study eye (ETDRS letters) Key secondary: Average change in BCVA from Baseline over the period Week 40 through Week 52	Ongoing: FPFV: 23-Jul-2018 Data cut-off date: 11-Nov-2020 (This study is ongoing. The date reported refers to the primary efficacy analysis at Week 52 of double-masked treatment period
B2302 (KITE)	Phase III, two-arm, randomized, double-masked, multicenter study assessing the efficacy and safety of brolucizumab versus aflibercept in adult patients with visual impairment due to diabetic macular edema	100 weeks	Total: (N= 360) Brolucizumab 6 mg: 5 x q6w loading then q12w/q8w maintenance (with option to extend treatment interval during second year) (N=179) Aflibercept 2 mg: 5 x q4w loading then q8w maintenance (N=181)	Primary: change from baseline in BCVA at Week 52 in the study eye (ETDRS letters) Key secondary: Average change from baseline in BCVA over the period Week 40 through Week 52 in the study eye	Ongoing: FPFV: 27-Jul-2018 Data cut-off date: 29-Jun-2020 (This study is ongoing. The date reported refers to the primary efficacy analysis at Week 52 of double-masked treatment period)

BCVA: Best-corrected visual acuity
ETDRS: Early Treatment Diabetic Retinopathy Study
Study B2301 and Study B2302 are 2-year studies and are currently ongoing. Data up to Week 52 are presented in the current submission
Source: [Tabular Listing of All Clinical Studies]

2.3.2. Pharmacodynamics

Brolucizumab functions by binding to human VEGF-A and thereby neutralizing its activity. The effect of brolucizumab on pharmacodynamic aspects of disease activity was assessed in two pivotal Phase III clinical studies ((CRTH258B2301) and (CRTH258B2302)) in the DME population. The effect of brolucizumab was evaluated functionally by the change in visual acuity (ETDRS letter score) and morphologically by changes in anatomical parameters (i.e., CSFT, presence of retinal fluid and vascular

leakage). In these studies, brolucizumab 6 mg demonstrated robust vision gain and clinically meaningful anatomical improvement.

The primary endpoint, measured by change from baseline in best corrected visual acuity (BCVA) at Week 52, demonstrated non-inferiority for brolucizumab compared to aflibercept despite fewer injections in brolucizumab 6 mg arms. In addition, a greater proportion of subjects with retinal fluid resolution was observed in the brolucizumab 6 mg compared to aflibercept 2 mg arm, with more than half of subjects (55.1% in (CRTH258B2301) and 50.3% in (CRTH258B2302)) in the brolucizumab 6 mg arm maintained on a q12w dosing interval at Week 52.

No direct measure of target engagement between brolucizumab and VEGF in the eye was determined, because it is not feasible to collect retina and RPE-choroid samples from human subjects. In addition, the systemic suppression of free VEGF was not determined.

Data in the marketing authorization application for brolucizumab in nAMD showed, increased levels of signaling through the VEGF pathway are associated with pathologic ocular angiogenesis and retinal edema and brolucizumab functions by binding to human VEGF-A and thereby neutralizing its activity. However, direct target engagement between brolucizumab and VEGF in the eye or systemic circulation was not assessed in the nAMD application nor this new indication submission as the concentration of VEGF in the serum is not known to be directly associated with the VEGF concentration in the eye.

2.3.3. Conclusions on clinical pharmacology

As in the initial Marketing Authorisation Application, no specific pharmacodynamic studies were conducted with brolucizumab. It is intended that intravitreal injection would allow adequate vitreous concentration to bind ocular VEGF. Nonclinical studies provided at the time of the MAA together with anatomical evaluation in Phase III studies suggest that brolucizumab, by binding VEGF, has well a PD effect on exudative fluid accumulation in the macula. The applicant's conclusions are thus supported.

2.4. Clinical efficacy

2.4.1. Main study(ies)

Pivotal studies B2301 and B2302

The clinical development is based on two pivotal studies: ***CRTH258B2301 (KESTREL study)*** and ***CRTH258B2302 (KITE study)***. The design of both Phase III studies is globally similar.

The Applicant conducted 2 randomized, double-masked, multicenter, active-controlled clinical trials to compare the efficacy and safety of brolucizumab 6 mg versus aflibercept 2 mg (Eylea®), in subjects with visual impairments due to Diabetic Macular Edema (DME). Both studies are conducted versus aflibercept 2 mg IVT (Eylea®).

The total studies duration was 100 weeks.

The main difference in study design were that KESTREL study included a brolucizumab 3 mg treatment arm in addition to the 6 mg arm, while the 6 mg dose only has been investigated in KITE study.

Methods

Study participants

Subjects ≥18 years of age with either type 1 or 2 controlled diabetes mellitus and visual impairment due to diabetic macular edema were included in the study population. The Applicants indicated that, in both studies, the study population was representative of the DME target population and was similar to the population of the pivotal VIVID and VISTA Phase III studies supporting the use of aflibercept in DME patients.

Main inclusion criteria were:

- Subjects with type 1 or type 2 diabetes mellitus and HbA1c of ≤10% at screening.
- Medication for the management of diabetes had to be stable within 3 months prior to randomization and is expected to remain stable during the course of the study
- Visual impairment due to DME with:
  - BCVA score between 78 and 23 letters, inclusive, using ETDRS visual acuity testing charts at a testing distance of 4 meters (approximate Snellen equivalent of 20/32 to 20/320) at screening and baseline
  - DME involving the center of the macula, with central subfield retinal thickness of (measured from RPE to ILM inclusively) ≥320 µm on SD-OCT at screening

If both eyes were eligible, the eye with the worse visual acuity was selected for study eye. However, the investigator could have selected the eye with better visual acuity, based on medical reasons or local ethical requirements.

Exclusion criteria included among others:

- Previous treatment with any anti-VEGF drugs or investigational drugs in the study eye
- Use of dexamethasone intravitreal implant (Ozurdex) or fluocinolone acetonide intravitreal implant (Iluvien) in study eye at any time. Prior use of other intraocular or periocular corticosteroids in the study eye is not an exclusion provided at least 6-month wash-out prior to baseline
- Laser photocoagulation (focal/grid or panretinal) in the study eye during the 3 month period prior to baseline
- Intraocular surgery including YAG laser in the study eye during the 3 month period prior to baseline
- History of vitreoretinal surgery in study eye
- Aphakia with the absence of posterior capsule in the study eye
- Active PDR in the study eye as per investigator
- Uncontrolled blood pressure defined as a systolic value ≥160 mmHg or diastolic value ≥100 mmHg at screening or baseline

Overall, the inclusion and the exclusion criteria are consistent with the target population.

However, it is to emphasize that the upper baseline BCVA limit for inclusion was 78 letters. It is supported that source population should reflect current usual practice where patients can be treated early in the course of the disease despite a mild impairment only. Nonetheless, given that 84 letters are equivalent to a 20/20 visual acuity, these patients have a less room for improvement, inferior to the mean change in BCVA at Week 52 for in primary analysis observed for every treatment groups.

Therefore, the limited room for improvement could be in favor of the non-inferiority. To that extent, subset analysis by BCVA at Baseline will be of importance, showing that conclusion are not changed while removing less impaired patients. As a note, the upper limit of 73 letters had been used in VISTA and VIVID studies to demonstrate the non-inferiority of Eylea compared to laser.

Regarding previous treatments, the population includes both treatment-naïve patients and subjects already treated by corticosteroids or laser. The 6-month wash-out period and the 3-month wash-out period prior respectively use of other intraocular or periocular corticosteroids and laser photocoagulation are considered acceptable.

Following a question on this point, the Applicant clarified that KESTREL and KITE studies were conducted in 40 countries globally, of which 22 were in Europe, and 44.5% (412/926) of the total study population were enrolled from these European countries. In KESTREL study, 29.7% (168/566) of the enrolled subjects were from European countries. In KITE study, 67.8% (244/360) of the enrolled subjects were from European countries. This appears sufficient to generalise the results to a European population.

Based on the study reports, the clinical overview and the clinical summary, it is no clear in which countries the two studies have been conducted. Thus, there are uncertainties whether the study population are representative enough of the European population. Therefore, the list of countries where subjects were enrolled, as well as the number of subjects per country, need to be provided and discussed.

Treatments

Dose and regimen

The Applicant stated the doses for brolucizumab are based on the Phase III brolucizumab studies in nAMD, wherein brolucizumab 6 and 3 mg doses showed comparable efficacy and safety profiles to existing anti-VEGFs with numerical advantages related to efficacy for the higher dose.

For both phase III studies, the Applicant had tested the 6 mg dose. Additionally, the 3 mg dose had been investigated in B2301 study. The Applicant emphasizes that it was to evaluate the dose-response following multiple dosing with brolucizumab in patients with DME.

Brolucizumab is for intravitreal injections (IVT), planned to be supply as sterile glass vials as well as pre-filled syringe.

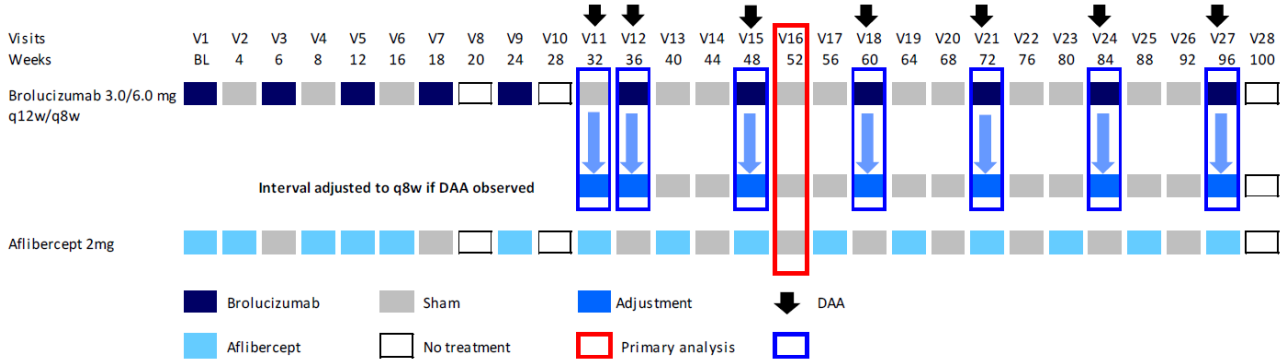
The comparator was aflibercept 2 mg for IVT (Eylea).

Patients in brolucizumab arms (3 mg and 6 mg) received 5 loading doses every 6 weeks (q6w) (Day 0, Week 6, Week 12, Week 18 and Week 24), followed by maintenance regimens every 12 weeks (q12w) or every 8 weeks (q8w) depending on the disease activity status. At the first round of assessment, the CHMP noted that *Pro Re Nata (PRN) neither Treat-and-Extend (T-&-E) had not been investigated. However, these treatment strategies are largely used in common practice to manage anti-VEGF IVT medication, especially to reduce the treatment burden*. The Applicant pointed out that an even more personalised regimen approach was assessed during year 2 of the KITE study with a 4-week extension to prolong the treatment interval from q8w to q12w, or q12w to q16w. Based on the masked investigator's discretion, a 4-week treatment interval extension could be made to the subject's treatment regimen at the time of Week 72. Considering the study duration (i.e. 100 weeks), starting more personalized treatment at Week 72, this however does not allow to fully investigate the adequacy of such individualized treatment in brolucizumab given the short period of assessment (e.g. only one cycle of treatment for patient under the q16w regimen). Thus, no strong conclusion can be drawn. The

Applicant is still encouraged to further investigate personalised regimen for brolucizumab in DME in additional studies.

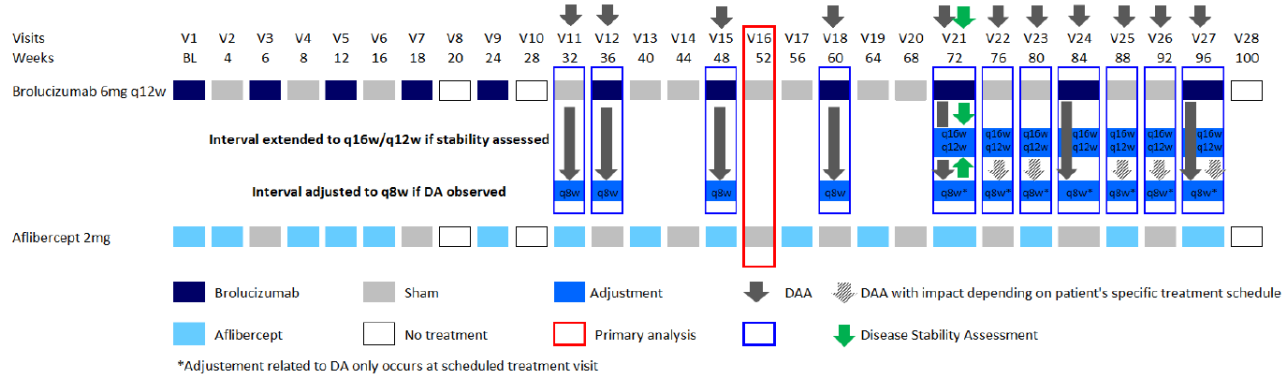
Patients in aflibercept arms received monthly 5 loading doses (Day 0, Week 4, Week 8, Week 12 and Week 16), followed by maintenance regimen every 8 weeks (q8w).

Figure 1: Dosing schedule in B2301



Source: [Study B2301 Wk52-Figure 9-2]

Figure 2: Dosing schedule in B2302



Source: [Study B2302 Wk52-Figure 9-2]

The Applicant indicates that the peak effect in BCVA gain and CSFT reduction observed after 6 weeks following a single intravitreal injection of brolucizumab 6 mg in early Phase I/II study in nAMD and the sustained disease control during the loading phase in nAMD Phase III studies were the basis for an extended interval between brolucizumab injections in the loading phase to 6 weeks in DME studies. Additionally, the Applicant explained that the positive nAMD Phase III study results support q12w/q8w regimen during the maintenance phase also for DME. Both, extended intervals in the initial treatment phase (loading regimen) and q12w/q8w dosing in the maintenance phase, aim at reducing the injection burden.

Assessment of disease activity

The suitability of the proposed q12w regimen, and assessment of the need for more frequent q8w treatment, was monitored through DAA (Disease Activity Assessment) conducted by the masked investigator. Subjects were to remain on the q12w regimen as long as the masked investigator did not identify DME disease activity at the DAAs, which, in the opinion of the investigator, required more frequent anti-VEGF treatment.

The presence of disease activity was determined by the masked investigator. The outcome of this assessment was captured as:

- ‘q8w-need’: identified disease activity which according to the masked investigator requires more frequent anti-VEGF treatment, e.g.: ≥5 letters loss in BCVA (compared to Week 28) which-based on anatomical parameters – is attributable to DME disease activity.
- ‘no q8w-need’: otherwise.

Further to a question from CHMP, the Applicant indicated that no defined exact criteria have been set for disease activity assessment in order to mimic real-world practice. While this is not a conservative approach, this can be understood. Additionally, it is acknowledged that the proportion of subjects in the brolucizumab 6 mg arm was maintained on a q12w regimen, meaning with no disease activity, was relatively similar across the two KITE and KESTREL studies. This suggest that no large variation in disease activity assessment occurred across investigators.

Rationale for choice of comparator

The Applicant justifies the choice of Aflibercept 2 mg as comparator being an established standard of care option for DME. It was chosen as comparator for this study due to the consistency of the approved label of aflibercept (Eylea®) for DME across many countries, especially EU and US.

Aflibercept is agreed as a relevant comparator as it is part of the standard of care for DME.

Objectives and outcomes/endpoints

The primary, secondary and exploratory objectives for the B2301 and B2302 studies are presented below along with their respective endpoints.

B2301 Study

Objective(s)	Endpoint(s)
Primary objective	**Endpoint for primary objective**
To demonstrate that brolucizumab is non-inferior to aflibercept with respect to the visual outcome after the first year of treatment	• Change from baseline in BCVA at Week 52
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
To demonstrate that brolucizumab is non-inferior to aflibercept with respect to visual outcome during the last 3 months of the first year of treatment	• Change from baseline in BCVA averaged over a period Week 40 to Week 52
To estimate the proportion of patients treated at q12w frequency with brolucizumab	• Proportion of patients maintained at q12w up to Weeks 52 & 100
To estimate the predictive value of the first q12w cycle for maintenance of q12w treatment with brolucizumab	• Proportion of patients maintained at q12w up to Weeks 52 & 100, within those patients that qualified for q12w at Week 36
To evaluate the functional and anatomical outcome with brolucizumab relative to aflibercept	• Change from baseline by visit up to Week 100 in BCVA and in parameters derived from SD-OCT, color fundus photography and fluorescein angiography
To evaluate the effect of brolucizumab relative to aflibercept on the DR status	• Change in ETDRS DRSS score up to Week 100
To assess the safety and tolerability of brolucizumab relative to aflibercept	• Incidence of ocular and non-ocular AEs, vital signs and laboratory values up to Week 100
To evaluate the effect of brolucizumab relative to aflibercept on patient-reported outcomes (VFQ-25)	• Change in patient reported outcomes (VFQ-25) total and subscale scores from baseline up to Week 100
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
To explore genetic factors that may influence disease phenotype or treatment response	• Details regarding endpoints and analysis related to this objective will be specified and presented in a separate document
To explore macular vascular pathology by OCT angiography	• Change of the status of macular capillaries • Subgroup analysis of visual outcome by baseline status
To explore peripheral retinal pathology by wide-field angiography and wide-field fundus photography imaging	• Baseline status of peripheral features relevant for DR severity grading at baseline and their changes

B2302 Study

Objective(s)	Endpoint(s)
Primary objective	**Endpoint for primary objective**
To demonstrate that brolucizumab is non-inferior to aflibercept with respect to the visual outcome after the first year of treatment	• Change from baseline in BCVA at Week 52
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
To demonstrate that brolucizumab is non-inferior to aflibercept with respect to visual outcome during the last 3 months of the first year of treatment	• Change from baseline in BCVA averaged over a period Week 40 to Week 52
To estimate the proportion of patients treated at q12w frequency with brolucizumab	• Proportion of patients maintained at q12w up to Weeks 52 & 100
To estimate the predictive value of the first q12w cycle for maintenance of q12w treatment with brolucizumab	• Proportion of patients maintained at q12w up to Week 52, within those patients that qualified for q12w at Week 36 • Proportion of patients maintained at q12w/q16w up to Week 100, within those patients that qualified for q12w at Week 36
To assess the potential to extend treatment intervals for brolucizumab patients during the second year of treatment	• Proportion of patients maintained on q16w up to Week 100 within the patients on q12w at Week 68 and on q16w at Week 76 • Proportion of patients re-assigned and maintained on q12w up to Week 100 within the patients on q8w at Week 68 and on q12w at Week 80 • Treatment status at Week 100
To evaluate the functional and anatomical outcome with brolucizumab relative to aflibercept	• Change from baseline by visit up to Week 100 in BCVA and in parameters derived from SD-OCT, color fundus photography and fluorescein angiography
To evaluate the effect of brolucizumab relative to aflibercept on the DR status	• Change in ETDRS DRSS score up to Week 100
To assess the safety of brolucizumab relative to aflibercept	• Incidence of ocular and non-ocular AEs, vital signs and laboratory values up to Week 100
To evaluate the effect of brolucizumab relative to aflibercept on patient-reported outcomes (VFQ-25)	• Change in patient reported outcomes (VFQ-25) total and subscale scores from baseline up to Week 100
To confirm the systemic brolucizumab exposure in patients with visual impairment due to DME	• Systemic brolucizumab concentration approximately 24 hours after initial and final loading phase doses
To assess the immunogenicity of brolucizumab over two years of treatment	• ADA status at baseline and up to Week 100
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
To explore genetic factors that may influence disease phenotype or treatment response	• Details regarding endpoints and analysis related to this objective will be specified and presented in a separate document
To explore macular vascular pathology by OCT angiography	• Change of the status of macular capillaries • Subgroup analysis of visual outcome by baseline status
To explore peripheral retinal pathology by wide-field angiography and wide-field fundus photography imaging	• Baseline status of peripheral features relevant for DR severity grading at baseline and their changes

Overall, objectives and endpoints are acceptable.

Testing the non-inferiority of brolucizumab compared to a current standard of care medication (i.e. Eylea®) for primary analysis appears relevant.

The mean change in BCVA from baseline is an acceptable primary endpoint with clinical relevance in DME. Likewise, the primary timepoint (i.e. 52 weeks) is reasonable in order to observe treatment effect with respect to the natural course of the disease. Additionally, the Applicant planned to assess the mean change in BCVA from Baseline averaged over the period Week 40 to Week 52, which is welcomed in the context of multiple regimens (i.e. q8w and q12w).

Third and fourth secondary endpoints are consistent since the Applicant want to show the suitability of the q12w regimen in the management of brolucizumab IVT. However, although endpoints on the

suitability of the q12w regimen are flagged as key secondary endpoints, there are not part of the hierarchical strategy given no testing analysis can be done; no comparison to aflibercept is possible, so results are descriptive only. Additionally, given that the regimen of the aflibercept arms was fixed, no comparison about treatment burden with current approved medication can be done.

The justified the ranking of the key secondary endpoints reporting that CSFT reduction was deemed to be more clinically impactful and more widely used than fluid resolution.

In response to a question by the CHMP, the Applicant has also included results at 100 weeks, that are reported below.

Sample size

Sample size

A sample size of 160 subjects per arm was considered for both studies B2301 and B2302 to allow the demonstration of the non-inferiority (non-inferiority margin of 4 ETDRS letters) of brolucizumab 6 mg or 3 mg (either treatment regimen) vs. aflibercept 2 mg with respect to the BCVA change from baseline at Week 52, with 90% power (disregarding the dependence within the sequential testing procedure, i.e., local power for 3 mg) at a one-sided alpha level of 0.025, assuming equal means and a common standard deviation of 11 letters. Assuming that averaging over the 4 time points would not lead to an increase in the standard deviation, a power of at least 90% could also be expected for its corresponding non-inferiority claim.

Considering a drop-out rate of 10%, 178 per arm were planned to be randomised. As a result, a total of 534 subjects were to be randomised in Study B2301 (3 arms) and 356 subjects in Study B2302 (2 arms).

Rationale for choice of non-inferiority margin

Non-inferiority testing related to the primary efficacy parameter BCVA in both studies was based on a margin of 4 letters for the change from baseline in BCVA at Week 52. According to the Applicant, this non-inferiority margin provided assurance that both absolute efficacy and efficacy relative to the active comparator aflibercept could be established and any proof of non-inferiority only occurred if the observed treatment differences were of no clinical relevance. The CHMP considers that this non-inferiority margin of 4 is too broad and therefore not acceptable. Such concern is however resolved by the results (see below).

Interim analyses

The analysis based on the Week 52 data (analysis included in this report) is the primary efficacy and safety analysis for both studies. The databases include all data up to Week 52 from when all randomized subjects have completed the Week 52 visit or terminated the study prior to (or at) Week 52.

Additional sample size considerations for evaluation of DRSS data across Studies B2301 and B2302

The evaluation of DRSS data in each study was not powered for non-inferiority testing, therefore pooling of DRSS data from the two studies (brolucizumab 6 mg, aflibercept 2 mg) was needed to provide sufficient power to robustly assess non-inferiority as per pre-defined analysis. In particular, data from these studies were pooled to support overall conclusions regarding the non-inferior efficacy of brolucizumab 6 mg in DR in subjects with DME compared to aflibercept, in terms of ≥ 2-step improvement in DRSS at Week 52, using a 10% non-inferiority margin on the difference in the proportion of subjects achieving ≥ 2-step improvement in DRSS at Week 52 between brolucizumab 6 mg and aflibercept 2 mg. With this approach, and assuming that 30% of subjects achieve ≥ 2-step improvement in DRSS at Week 52 in both treatment groups, a sample size of 356 subjects in each group provides 82% power for non-inferiority testing.

Randomisation

Study B2301:

At baseline visit, all eligible subjects were randomized via IRT to one of the three treatment arms (brolucizumab 3 mg, brolucizumab 6 mg and aflibercept 2 mg), in a ratio of 1:1:1. Stratification for Japanese ethnicity (Japanese vs. non-Japanese) was performed.

Study B2302:

At baseline visit, all eligible subjects were randomized via IRT to one of the two treatment arms (brolucizumab 6 mg and aflibercept 2 mg), in a ratio of 1:1. Stratification for systemic exposure sampling was performed.

In the 2016 Scientific Advice (EMA/CHMP/SAWP/104791/2016), the Applicant was advised to consider a stratification of the randomisation by HbA1c level. This recommendation was not followed for either studies as the only stratification factor is for Japanese vs non-Japanese (B2301) or systemic exposure sampling (B2302).

Therefore, the impact of any imbalance of HbA1c levels at baseline should be considered as well as the consistency of subgroup analyses by baseline HbA1c.

Blinding (masking)

Since the treatment schedule was different between the brolucizumab and aflibercept arms, the following procedures were applied to ensure double-masking and limit bias in the conduct and interpretation of each study:

In addition to every 4-week visits for all subjects for 2 years, extra visits were scheduled at Weeks 6 and 18 for each treatment arm.

- Active/sham injections at each protocol visit to establish an identical treatment schedule across treatment arms, except at Weeks 20, 28 and 100 visits (no scheduled treatment for any arm).
- To fulfil the double-masking requirement, each investigational site had masked and unmasked staff. The investigator who performed the injection was unmasked to the treatments as were any other site personnel who had been delegated responsibility for working with the IP. The unmasked site personnel and unmasked injecting investigator did not perform BCVA, complete ophthalmic examination (with the exception of post- injection safety assessment), DAAs or administer the VFQ-25. Also, the unmasked site personnel and unmasked injecting physician did not perform assessment of any ocular or non-ocular safety parameters, or assess causality of AEs for subjects during the course of the study except an event reported immediately following IVT injection. Once the designated roles were determined, the unmasked investigator/site personnel roles were not switched at any time after randomization to masked role. Every effort was made to limit the number of unmasked study personnel to ensure the integrity of this masked study.
- The unmasked investigator/site personnel assessed subject safety immediately following injection.
- Unmasked monitors and unmasked global clinical team members were available to perform study medication accountability and to deal with study issues involving the unmasked investigator or unmasked site staff. Remaining members of the Sponsor Study team were masked to treatment assignments until all randomized subjects completed the primary endpoint evaluation at the Week 52 visit (or terminated the study prior to or at Week 52).

- An independent, masked review of fundus photography, fluorescein angiography and OCT images for subjects enrolled in the study was performed at a CRC.
- DAA was performed for each treatment arm by the masked investigator at the protocol specified visits.
- Treatment masking will remain intact for all subjects, masked investigators and masked site personnel until the end of the study, except in the case of subject emergencies.

The use of sham injections at each protocol visit to establish an identical treatment schedule across treatment arms is appropriate. The above double-masking process and associated requirements are deemed appropriate.

Statistical methods

Analysis populations (both studies B2301 and B2302)

The following analysis sets were defined:

- All enrolled set: included all subjects who signed informed consent.
- Randomized set: included all randomized subjects. Subjects were analysed according to the treatment assigned to at randomization.
- Full analysis set (FAS): included all randomized subjects who received at least one IVT injection of the study treatment. Subjects were analysed according to the treatment assigned to at randomization.
- Per-protocol set (PPS): subset of the FAS that excluded subjects with important protocol deviations and analysis restrictions that were expected to majorly affect the validity of the assessment of efficacy and/or safety at Week 52 (e.g. lack of compliance [including missed treatments and treatment misallocation], missing data, prohibited concomitant medication and deviations from inclusion/exclusion criteria). Confounded data or discontinuation from study treatment due to lack of efficacy and/or safety did not constitute a reason for exclusion from the PPS.
- Safety set (SAF): included all subjects who received at least one study drug IVT injection. Subjects in the SAF were analysed according to the treatment arm from which they received majority of treatments up to and including Week 48.

Multiplicity adjustment

The multiplicity adjustment procedures differ between study B2301 and study B2302.

Study B2301

The objective related to the primary and first key secondary endpoints was to demonstrate non-inferiority of brolucizumab to aflibercept with respect to change from baseline in BCVA, considering a margin of 4 ETDRS letters.

Let:

B6 = Brolucizumab 6 mg - 5 x q6w loading then q12w/q8w maintenance

B3 = Brolucizumab 3 mg - 5 x q6w loading then q12w/q8w maintenance

A = Aflibercept 2 mg - 5 x q4w loading then q8w maintenance

The following non-inferiority hypotheses were used in the analysis and were related to a non-inferiority margin of 4 letters:

H01: μ B6 - μ A $\leq$ -4 letters vs. HA1: μ B6 - μ A > -4 letters

H02: φB6 – φA $\leq$ -4 letters vs. HA2: φB6 – φA > -4 letters

H03: μ B3 - μ A $\leq$ -4 letters vs. HA3: μ B3 - μ A > -4 letters

H04: φB3 – φA $\leq$ -4 letters vs. HA4: φB3 – φA > -4 letters

BCVA at Week 52 in the brolucizumab 6 mg, brolucizumab 3 mg and aflibercept 2 mg arms, respectively; φB6, φB3 and φA were the corresponding unknown true mean changes from baseline in BCVA averaged over the period Week 40 to Week 52 in the brolucizumab 6 mg, brolucizumab 3 mg and aflibercept 2 mg arms, respectively.

Two-sided 95% CI for the LS mean difference (brolucizumab - aflibercept) were presented in letters. Non-inferiority was considered established if the lower limit of the corresponding 95% CI was greater than -4 letters. P-value for treatment comparison (two-sided) and p-value for non-inferiority (4 letter margin) (one-sided) were presented.

These four alternative hypotheses were tested sequentially in the order of their numbering (HAn, n=1, 2, 3, 4), i.e., confirmatory testing of the second, third or fourth hypotheses required rejection of each preceding null hypothesis. In this setting, each hypothesis was assessed at a one-sided significance level of 0.025, while keeping the global type I error rate at 0.025.

No hypothesis was to be tested for the additional key secondary efficacy endpoints.

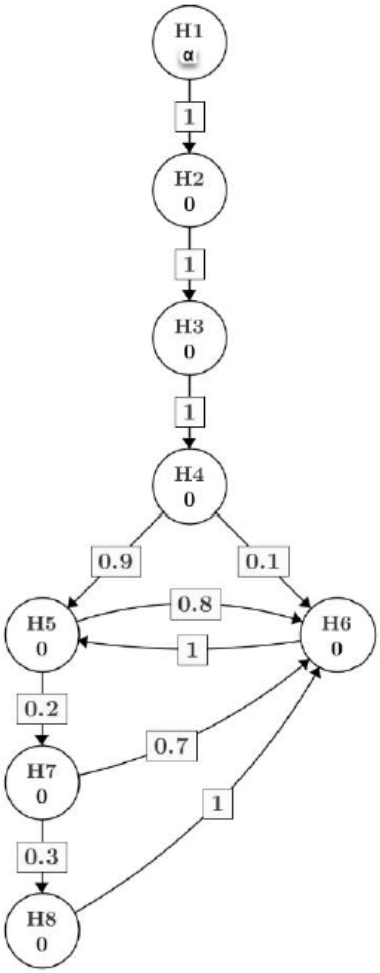
However, superiority testing of hypotheses for additional secondary endpoints was to be performed on the condition that proof of non-inferiority related to BCVA was successful for the four non-inferiority hypotheses (H1 to H4) specified for the primary and first key secondary endpoints.

The additional efficacy hypotheses are linked to the below endpoints:

- H5. Average change from baseline in CSFT over the period Week 40 through Week 52 in the study eye
- H6. Absence of fluid in the study eye at Week 52 (no=absence of SRF and IRF)
- H7. Change from baseline in CSFT at Week 4 in the study eye
- H8. Average change from baseline in BCVA over the period Week 40 through Week 52 in the study eye.

All tests were one-sided tests for superiority of brolucizumab 6 mg vs. aflibercept 2 mg only (not brolucizumab 3 mg vs. aflibercept 2 mg).

The primary and relevant secondary efficacy endpoints were to be assessed using a multiple testing procedure resulting from the graphical approach of Bretz et al (Bretz et al 2009) with an initial one-sided significance level of 0.025. The family-wise type I error rate was controlled at the one-sided 2.5% level across the tested null hypotheses using the closed testing procedure implemented through the graphical method as specified in the figure below.



Hypotheses H_1,..., H_8 are represented by circles with the initial significance levels. The arrow represents the direction in which the significance level is propagated throughout the graph and the number in the square box represents the proportion of the propagated significance level.

The first four hypotheses were to be tested sequentially in the order of their numbering (Hn, n=1, 2, 3, 4), i.e., confirmatory testing of the second, third or fourth hypotheses requires rejection of each preceding null hypothesis.

If each of the first four null hypotheses was rejected at a one-sided significance level of 0.025, the entire alpha was to be distributed between the null hypotheses related to the superiority testing of H5 (90% of 0.025 = 0.0225), and H6 (10% of 0.025 = 0.0025). This split was chosen by balancing out prior expectations about the study outcomes and the clinical importance of the endpoints.

The multiplicity adjustment procedure used for the study itself is in principle deemed appropriate. The additional superiority hypotheses based on secondary endpoints (H5 to H8 for study B2301, H3 to H5 for study B2302) were introduced with a SAP amendment. Because of the late timing of the change, and considering the complexity of the masking process, this could have raised a potential issue of type I error inflation. However, it is acknowledged that no hypotheses were rejected beyond H2 in study B2301. In study B2302, no hypotheses were rejected beyond H3 (CSFT), and the significance of the CSFT endpoint was not replicated in Study B2301. Therefore this raises no concerns.

Study B2302

The objective related to the primary and first key secondary endpoints was to demonstrate noninferiority of brolucizumab to aflibercept with respect to the change from baseline in BCVA, considering a margin of 4 ETDRS letters.

Let:

B = Brolucizumab 6 mg - 5 x q6w loading then q12w/q8w maintenance

A = Aflibercept 2 mg - 5 x q4w loading then q8w maintenance

The following non-inferiority hypotheses were used in the analysis and were related to a noninferiority margin of 4 letters:

H01: μ B - μ A $\leq$ -4 letters vs. HA1: μ B - μ A > -4 letters

H02: ϕ B - ϕ A $\leq$ -4 letters vs. HA2: ϕ B - ϕ A > -4 letters

where μB and μA were the corresponding unknown true mean changes from baseline in BCVA at Week 52 in the brolucizumab and aflibercept arms, respectively; φB and φA were the corresponding unknown true mean changes from baseline in BCVA averaged over the period Week 40 to Week 52 in the brolucizumab and aflibercept arms, respectively.

Non-inferiority was considered established if the lower limit of the corresponding 95% CI was greater than -4 letters. P-value for treatment comparison (two-sided) and p-value for non-inferiority (4-letter margin) (one-sided) were presented.

These two alternative hypotheses were tested sequentially in the order of their numbering (HAn, n=1, 2), i.e., confirmatory testing of the second hypothesis required rejection of the first null hypothesis. In this setting, each hypothesis was assessed at a one-sided significance level of 0.025, while keeping the global type I error rate at 0.025.

No hypothesis was to be tested for the additional key secondary efficacy endpoints.

However, superiority testing of hypotheses for additional secondary endpoints was performed on the condition that proof of non-inferiority related to BCVA was successful for the two hypotheses (H1 and H2) for the primary and first key secondary endpoints.

The additional efficacy hypotheses are linked to the below endpoints:

- H3. Average change from baseline in CSFT over the period Week 40 through Week 52 in the study eye
- H4. Average change from baseline in BCVA over the period Week 40 through Week 52 in the study eye
- H5. Fluid-status 'yes/no' in the study eye at Week 52 (no= absence of SRF and IRF).

All tests were one-sided tests for superiority of brolucizumab vs. aflibercept.

The alternative hypotheses were to be tested hierarchically in the order H3, then H4, then H5, i.e., confirmatory testing of the hypothesis required rejection of the previous null hypothesis. In this setting, each hypothesis was assessed at a one-sided significance level of 0.025, while keeping the global type I error rate at 0.025.

Primary and first key secondary analyses (both studies B2301 and B2302)

The primary endpoint is the change from baseline in BCVA at Week 52 in the study eye (ETDRS letters).

The first key secondary endpoint is the average change from baseline in BCVA over the period Week 40 through Week 52 in the study eye. For each subject, this endpoint is defined as the average of the changes from baseline to Weeks 40, 44, 48 and 52.

The primary analysis of the primary and first key secondary endpoints was based on the FAS with last observation carried forward (LOCF) imputation of missing or censored BCVA values.

The primary estimand for the primary endpoint included the following components:

- Population: Subjects with visual impairment due to DME as per the inclusion/exclusion criteria
- Endpoint: The primary endpoint is the change from baseline in BCVA at Week 52.
- Treatment of interest: The randomized study treatment (brolucizumab or aflibercept)
- The handling of the remaining intercurrent events as follows:
    - Study discontinuation due to any reason: data imputed with LOCF
    - Treatment discontinuation due to any reason: use all the data
    - Data after the start of alternative DME treatment will be censored
- Summary measure: Difference in the change from baseline in BCVA at Week 52 between brolucizumab and aflibercept treatment arms.

The primary estimand for the first key secondary endpoint had similar components.

It is noted that both the primary estimand on the FAS and the supplemental estimand on the PPS (see below) include a mix of treatment policy strategies and hypothetical strategies depending on the intercurrent event (ICE) considered. In order to further aid the interpretation of the results, the Applicant was requested to perform supplementary analyses based on the following estimands:

- Additional estimand A: A treatment policy is followed for all ICEs, i.e. all data are included in the analysis regardless of ICEs. This estimand will be aimed at more closely following the ITT principle and corresponding analyses should be performed on the FAS.

- Additional estimand B: A hypothetical strategy is followed for all ICEs (i.e. for study discontinuation, treatment discontinuation, start of alternative DME treatment, start of prohibited medications or procedures).

Furthermore it was requested that the frequency and timing of each ICE were summarised by treatment group.

Other secondary analyses (both studies B2301 and B2302)

Continuous endpoints:

The continuous secondary endpoints related to BCVA and CSFT was analysed using ANOVA models. The estimates of least square means for each treatment and for the treatment differences brolucizumab – aflibercept, including 95% CIs for the treatment differences, were presented.

For the ANOVA analysis of BCVA-related endpoints, baseline BCVA (≤65, >65 letters) and age category (<65, ≥65 years) were considered as class variables. For the ANOVA analysis of CSFT, baseline CSFT (<450, ≥450-<650, ≥650 μ m) were used instead of baseline BCVA as a class variable.

Categorical variables:

For binary endpoints, frequency tables (count and percentage) were provided by time point. In addition, proportions and treatment differences in proportions along with 95% CIs were presented for each time point using a logistic regression with treatment, the corresponding baseline status (similar to the ones specified for the ANOVA models) and age categories as fixed effects.

Time-to event variables:

Time-to-event variables such as the time to achieve gain in BCVA of ≥5 (respectively ≥10 and ≥15) letters from baseline (or reaching a score of 84 or more) were analysed using KM analysis. KM estimates on

percent of subjects who achieve gain, together with 95% CI were presented by visit. The median time (95% CI) to gain was also constructed by treatment arm. KM curves presenting the cumulative probability of subjects with gain of ≥5 (respectively ≥10 and ≥15) letters from baseline were provided by treatment arm.

Proportions of subjects maintained at q12w up to week 52:

The estimate for the proportion of subjects maintained at q12w up to week 52 was derived from Kaplan-Meier time-to-event analyses for the event 'first q8w-need', applying a 'q8w-need' allocation in case of missing or confounded data attributable to lack of efficacy and/or lack of safety.

Supplementary analysis (both studies B2301 and B2302)

Supplementary estimand on the PPS:

The target population, the primary endpoint, the treatment of interest and the summary measure of the supplementary estimand were the same as for the primary estimand. In addition to the censoring of data after a switch to alternative DME treatment (described for the primary estimand), the estimand based on the PPS censored data after prohibited medications or procedures. Imputation used the last observation collected before the corresponding intercurrent event (ICE).

The supportive analysis on the supplementary estimand applied the same LOCF/ANOVA method as for the primary estimand.

Sensitivity analyses of the primary endpoint (both studies B2301 and B2302)

Mixed model for repeated measures (MMRM) assuming missing at random (MAR) using observed data only (including censoring of BCVA values collected after the start of alternative DME treatment). The MMRM included treatment, visit, baseline BCVA category, age category and treatment by visit interaction as fixed-effect terms, and visit as a repeated measure. An unstructured covariance matrix was used to model the within-subject error. In this analysis, data collected after the switch to alternative DME treatment in the study eye was censored.

As the analyses presented all assumed data missing at random, but a missing-not-at-random mechanism is also clinically credible in this setting, *the Applicant was requested to perform tipping point analyses exploring more conservative scenarios for missing data in the brolucizumab arm for primary and first key secondary endpoints, and to comment on the results. These analyses were repeated based on above estimands A and B. The tipping point analyses (see results below) indicated that a relatively large negative shift would be required for the non-hypothesis to be accepted for the primary endpoint. Based on these results, the impact of MNAR data on the efficacy results should be limited and is not expected to impact the study conclusions*

Subgroup analyses (both studies B2301 and B2302)

The subgroups of interest are specified below:

- Age category (<65, ≥65 years)
- Gender (male, female)
- Diabetes type (Type 1, Type 2)
- Baseline HbA1c (<7.5, ≥7.5%)
- Baseline BCVA categories (≤65, >65 letters)
- Duration of DME since the primary diagnosis (≤3, >3-<12, ≥12 months)
- DME type (focal, diffuse) as per CRC

- Baseline CSFT (<450, ≥450-<650, ≥650 µm)
- Baseline status of IRF (presence, absence)
- Baseline status of SRF (presence, absence)
- Ethnicity (Japan, non-Japan).

Subgroup analyses were performed for the primary and key secondary efficacy variables only.

Changes in planned analyses

Study B2301

The protocol was amended 3 times. Changes with a relevant impact on statistical methods are included below.

Protocol amendment	Changes to statistical methods
V02 11-Feb-2020	Purpose and timing of interim analyses/design adaptations were updated for the primary analysis to be conducted when first 534 randomised subjects have completed their Week 52 visit or terminated study prior to Week 52 Clarification regarding analysis of Japanese subjects Clarification regarding treatment masking
V03 12-Jun-2020	Modifications to align with ICH E9 (R1) guideline Changes to account for COVID-19 impact Endpoints moved from secondary to exploratory

Changes introduced in the SAP:

The main change introduced in the SAP was included as part of SAP amendment V1.0 (dated 26-Nov-2020), which introduced hypotheses testing in relation to additional secondary endpoints. Indeed, hypotheses H5 to H8 described in the above multiplicity adjustment section were not part of the fixed sequence testing procedure described in the protocol. The amendment also added analyses to cover the potential impact of the COVID-19 pandemic, and was finalized prior to database lock.

In addition, the SAP amendment reflected the change in the timing of the analyses, which occurred when all subjects had completed the Week 52 visit instead of after the first 534 randomized subjects had completed the Week 52 visit.

Study B2302

The protocol was amended twice. Changes with a relevant impact on statistical methods are included below.

Protocol amendment	Changes to statistical methods
V01 18-May-2018	Added clarification on the framework of analysis on study information collected from withdrawn subjects The PK of aflibercept was removed from testing and analysis
V02 11-Jun-2020	Modifications to align with ICH E9 (R1) guideline

	Changes to account for COVID-19 impact Endpoints moved from secondary to exploratory Clarification regarding treatment masking

Changes introduced in the SAP:

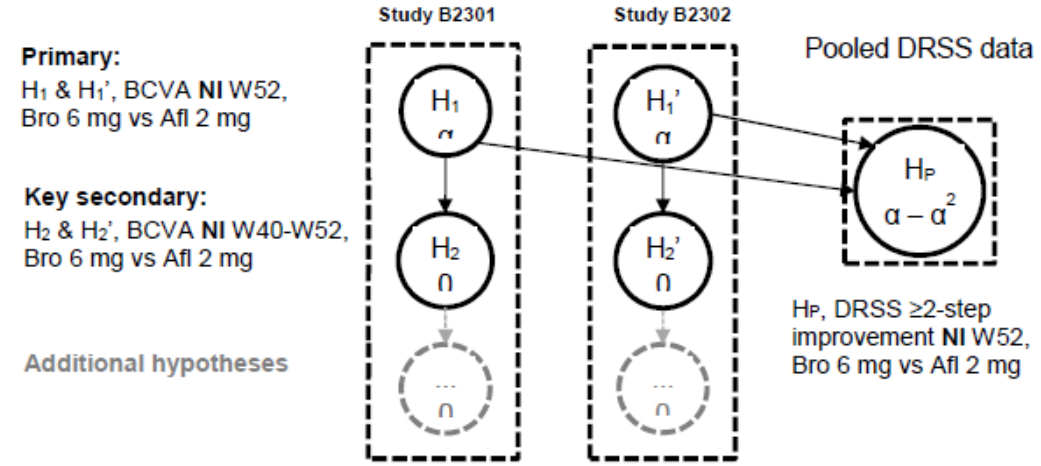
The main change introduced in the SAP was included as part of SAP amendment V1.1 (dated 17-Aug-2020), which introduced hypotheses testing in relation to additional secondary endpoints. Indeed, hypotheses H3 to H5 described in the above multiplicity adjustment section were not part of the fixed sequence testing procedure described in the protocol. The amendment also added analyses to cover the potential impact of the COVID-19 pandemic, and was finalized prior to database lock.

Pooled analysis across studies B2301 and B2302

For the purpose of assessing the potential benefit of treatment with brolucizumab 6 mg in a larger group of subjects with DME on the underlying DR, pooled data (E-db) from Study B2301 and Study B2302 for the secondary endpoint related to ≥2-step improvement from baseline in DRSS at Week 52 was analysed.

The multiple testing procedure followed the approach described in Bretz et al (2019), as shown in the figure below, and was pre-specified in the analysis plan for the SCE and finalised prior to the database lock of Study B2301 and Study B2302.

Figure: Multiple testing procedure (DR in subjects with DME)



NI = non-inferiority; W40 = Week 40; W52 = Week 52, Bro 6 mg = brolucizumab 6 mg, Afl 2 mg = aflibercept 2 mg

The primary and first key secondary hypotheses related to the primary and first key secondary endpoints, change from baseline in BCVA at Week 52 (H1 and H1') and averaged change in BCVA over the period Week 40 to Week 52 (H2 and H2'), respectively, were tested in hierarchical order within each study.

To ensure evidence of independent substantiation and replication, only if both studies B3201 and B2302 independently rejected the null hypothesis for the primary endpoint in a one-sided statistical test with p-value ≤0.025 (H1 and H1'), would the DRSS endpoint, ≥2-step improvement from baseline in DRSS at Week 52, be assessed for non-inferiority compared to aflibercept 2 mg using the pooled data of Study B2301 and Study B2302, and a 10% non-inferiority margin on the difference in proportion of subjects achieving ≥2-step improvement from baseline in DRSS at Week 52 between brolucizumab 6 mg and aflibercept 2 mg. More precisely, following Bretz et al (2019), non-inferiority in the DRSS endpoint could be established through a one-sided statistical test with a p-value ≤0.024375 (=0.025-0.0252). According

to the Applicant, the subtraction of α2 is required to allow for independent testing of the DRSS outcome from the outcomes of the first key secondary endpoint in the testing strategy for the individual studies, change from baseline in BCVA averaged over Week 40 to Week 52 (H2 & H2').

The Applicant provides the following justification for this approach: at the study level, the Type I error rate was controlled at the level 0.025 (one-sided), whereas at the submission level, the approach implemented ensured that the Type I error rate was controlled at the level 0.0252 (α2) for the primary hypotheses following the replication principle, and at ≤0.025 when considering all endpoints under all possible configurations of true and false null hypotheses, including that pertaining to the DRSS endpoint.

The analysis of difference in proportions between brolucizumab and aflibercept treatment groups used a logistic regression with treatment, the corresponding baseline DRSS (12-level scale ≤4, ≥5), age category (<65, ≥65 years) and study (B2301, B2302) as fixed effects.

The one-sided non-inferiority p-value and 95% CI for the difference will be calculated using bootstrap.

Each study has its own multiple testing procedure according to the graphical approach described previously. These study-specific multiple testing procedures do not include the DRSS endpoint at any step in the process.

Instead, the DRSS endpoint (≥2-step improvement from baseline in DRSS at Week 52) is tested outside of the study-specific testing procedures, using pooled data from Study B2301 and B2302. This is a non-inferiority test for the comparison of brolucizumab 6mg vs aflibercept 2 mg, using a 10% non-inferiority margin. The pooled non-inferiority test is only performed if both studies B3201 and B2302 reject their primary null hypothesis.

This three branch procedure, described by Bretz et al (2019), was specified in the SCE analysis plan prior to each study database lock. It is acknowledged that some considerations of type I error control at different levels can be derived from this approach. Each study has its own type I error control corresponding to the study-specific testing procedure, which does not include DRSS. A control of the type I error at "submission level" and across secondary endpoints is introduced with this approach. However this is deemed questionable. First, it is noted that the 2.5% one-sided type I error control that is claimed across secondary endpoints (at submission level) implies that any test performed at study level requires replication across both studies to reject any hypothesis. Therefore, and as would be generally expected, any finding that is not replicated across both pivotal trials should be removed from the SmPC. More importantly, this submission-level type I error control is not relevant to the study family wise error control. As a consequence, it is challenging to draw any meaningful conclusions regarding the control of the type I error within or across studies.

As noted by the Applicant, the same approach was followed for another product from the same Applicant in multiple sclerosis . BSWP advice had been sought on the issue. Despite the testing procedure being considered dubious (for the above reasons), the issue was not pursued and the pooled analysis was accepted for assessment with the following recommendation: "Careful interpretation of results based on achieved significance levels and clinical relevance by CHMP is warranted." The same advice applies to the present procedure.

The proportion of patients for which the DRSS endpoint was imputed due to missing or censored data is unclear. The Applicant was requested to clarify the proportion of imputed values by treatment group and by reason for imputation (i.e. missing, censored following start of DME treatment). A sensitivity analysis was provided where missing/censored values were counted as failures (non-improvement). The sensitivity analyses with missing/censored values imputed as failures showed lower improvements rates in both treatment arms, with a treatment difference that remained consistent with the CSR results.

Results

Participant flow

B2301 Study

Of a total of 873 subjects who were screened, 566 subjects were randomized in a 1:1:1 ratio to the brolucizumab 6 mg (n=189) or 3 mg (n=190) arms, or to the aflibercept 2 mg arm (n=187) between 30-Jul-2018 and 14-Nov-2019, and 307 subjects were not randomized due to screen failures.

Overall, 25 subjects (13.2%) in the brolucizumab 6 mg arm, 23 subjects (12.1%) in the brolucizumab 3 mg arm, and 18 subjects (9.6%) in the aflibercept 2 mg arm discontinued study treatment prior to or at Week 52; of these subjects who discontinued study treatment, 7 subjects in the brolucizumab 6 mg arm, 4 subjects in the brolucizumab 3 mg arm and 3 subjects in the aflibercept 2 mg arm remained in the study up to Week 52 after being discontinued from treatment

A total of 18 subjects (9.5%) in the brolucizumab 6 mg arm, 19 subjects (10.0%) in the brolucizumab 3 mg arm and 15 subjects (8.0%) in the aflibercept 2 mg arm discontinued the study prior to or at Week 52.

Table 1: Subject disposition of the study B2301 up to Week 52 (All Enrolled Set)

Disposition/Reason	Brolucizumab 3 mg n (%)	Brolucizumab 6 mg n (%)	Aflibercept 2 mg n (%)	Overall n (%)
All enrolled				873
Screening failure/Not randomized				307
All randomized	190	189	187	566
Randomized and treated	190 (100)	189 (100)	187 (100)	566 (100)
Completed Week 52 [1]	162 (85.3)	154 (81.5)	162 (86.6)	478 (84.5)
Ongoing, did not complete Week 52 [2]	9 (4.7)	17 (9.0)	10 (5.3)	36 (6.4)
Discontinued the study prior to or at Week 52	19 (10.0)	18 (9.5)	15 (8.0)	52 (9.2)
Adverse event	5 (2.6)	2 (1.1)	5 (2.7)	12 (2.1)
Death	1 (0.5)	5 (2.6)	2 (1.1)	8 (1.4)
Lost to follow-up	3 (1.6)	1 (0.5)	3 (1.6)	7 (1.2)
Physician decision	1 (0.5)	0	0	1 (0.2)
Progressive disease	0	1 (0.5)	0	1 (0.2)
Protocol deviation	1 (0.5)	0	1 (0.5)	2 (0.4)
Subject decision	8 (4.2)	9 (4.8)	4 (2.1)	21 (3.7)
Discontinued the study treatment prior to or at Week 52	23 (12.1)	25 (13.2)	18 (9.6)	66 (11.7)
Adverse event	7 (3.7)	4 (2.1)	6 (3.2)	17 (3.0)
Death	1 (0.5)	3 (1.6)	2 (1.1)	6 (1.1)
Lost to follow-up	3 (1.6)	3 (1.6)	3 (1.6)	9 (1.6)
Physician decision	3 (1.6)	2 (1.1)	0	5 (0.9)
Pregnancy	0	1 (0.5)	0	1 (0.2)
Protocol deviation	2 (1.1)	2 (1.1)	2 (1.1)	6 (1.1)
Subject decision	7 (3.7)	10 (5.3)	5 (2.7)	22 (3.9)

All enrolled = total number of subjects who consented.
Mis-randomized subjects are included in "Screening failure/Not randomized" category.
Percentages (%) are calculated based on "n" from "All randomized" category.
The reason for discontinuation as given by the investigator in the CRF.
Study discontinuations are included in treatment discontinuation category.
[1] Completed Week 52 = subjects have Week 52 visit.
[2] Subjects missed Week 52 visit, but remain in study at the time of Week 52 cut-off.
Early treatment discontinuation visit is derived based on subjects' last attended visit.
Source: Table 14.1-1.1

B2302 Study

Of a total of 480 subjects who were screened, 360 subjects were randomized in a 1:1 ratio to brolucizumab 6 mg arm (n=179) or aflibercept 2 mg arm (n=181) between 10-Aug-2018 and 02-Jul-2019, and 120 subjects were not randomized due to screen failures.

Overall, 19 subjects (10.6%) in the brolucizumab arm and 15 subjects (8.3%) in the aflibercept arm discontinued the study treatment; out of these, 2 subjects (1.1%) in the brolucizumab arm and 3 subjects (1.6%) in the aflibercept arm remained in the study up to Week 52 after being discontinued from treatment.

A total of 17 subjects (9.5%) in the brolucizumab arm and 12 subjects (6.6%) in the aflibercept arm discontinued the study prior to or at Week 52.

Table 2: Subject disposition of the study B2302 up to Week 52 (All Enrolled Set)

Disposition/Reason	Brolucizumab 6 mg n (%)	Aflibercept 2 mg n (%)	Overall n (%)
All enrolled	-	-	480
Screening failure/Not randomized	-	-	120
All randomized	179	181	360
Randomized and treated	179 (100)	181 (100)	360 (100)
Completed Week 52 [1]	145 (81.0)	152 (84.0)	297 (82.5)
Ongoing, did not complete Week 52 [2]	17 (9.5)	17 (9.4)	34 (9.4)
Discontinued the study prior to or at Week 52	17 (9.5)	12 (6.6)	29 (8.1)
Adverse event	4 (2.2)	3 (1.7)	7 (1.9)
Death	3 (1.7)	2 (1.1)	5 (1.4)
Lost to follow-up	1 (0.6)	1 (0.6)	2 (0.6)
Physician decision	1 (0.6)	2 (1.1)	3 (0.8)
Subject decision	8 (4.5)	4 (2.2)	12 (3.3)
Discontinued the study treatment prior to or at Week 52	19 (10.6)	15 (8.3)	34 (9.4)
Adverse event	7 (3.9)	7 (3.9)	14 (3.9)
Death	3 (1.7)	1 (0.6)	4 (1.1)
Lost to follow-up	1 (0.6)	1 (0.6)	2 (0.6)
Physician decision	2 (1.1)	0	2 (0.6)
Protocol deviation	1 (0.6)	2 (1.1)	3 (0.8)
Subject decision	5 (2.8)	4 (2.2)	9 (2.5)

All enrolled = total number of subjects who consented.
Mis-randomized subjects are included in "Screening failure/Not randomized" category.
Percentages (%) are calculated based on "n" from "All randomized" category.
The reason for discontinuation as given by the investigator in the CRF.
Study discontinuations are included in treatment discontinuation category.
[1] Completed Week 52 = subjects have Week 52 visit.
[2] Subjects missed Week 52 visit, but remain in the study at the time of Week 52 cutoff.
Early treatment discontinuation visit is derived based on subjects' last attended visit.
Source: Table 14.1-1.1

Overall, the participant flow does not raise concerns. The proportion of subject's discontinuation is acceptable and it remains well balanced across the groups.

Recruitment

B2301 Study

The first subject for this study was screened on 30-Jul-2018 and the last subject on 14-Nov-2019.

B2302 Study

The first subject for this study was screened on 10-Aug-2018 and the last subject on 02-Jul-2019.

Conduct of the study

B2301 Study

The study protocol was amended 3 times. Main changes were:

- Changes in relation to emerging safety issue are:
  - Information was added to describe a new safety signal from post-marketing case reports.

- Additional guidance was added emphasizing that if any sign of intraocular inflammation is present, an IVT injection must not be performed and subjects should be treated for intraocular inflammation according to clinical practice. Additional examination and assessments included to fully characterize cases of intraocular inflammation were made.
- Changes were incorporated to address the COVID- 19 pandemic.

- Three endpoints were moved from Secondary to Exploratory.
- Purpose and timing of interim analyses/design adaptations were updated for the primary analysis to be conducted when the first 534 randomized subjects have completed their Week 52 visit or terminated the study prior to Week 52.
- Clarification that data for the additional subjects randomized in Japan beyond the study target of 534 subjects was to be analyzed once these subjects had completed their Week 52 visit or terminated the study prior to Week 52.
- Details were added regarding the primary Week 52 analysis and additional analyses to allow for consistency assessment of data between Japanese and non-Japanese subjects.
- Inclusion criterion no. 5 was revised to allow enrollment of subjects with central subfield retinal thickness cut-off value on SD-OCT of ≥320 µm instead of ≥340 µm.
- The assessment schedule table was corrected according to protocol body text and adjustment of appearance for clarity.

B2302 Study

The study protocol was amended twice. Main changes were:

- Changes in relation to emerging safety issue are:
  - Information was added to describe a new safety signal from post-marketing case reports.
  - Additional guidance was added emphasizing that if any sign of intraocular inflammation is present, an IVT injection must not be performed and subjects should be treated for intraocular inflammation according to clinical practice. Additional examination and assessments included to fully characterize cases of intraocular inflammation were made.
  - Changes were incorporated to address the COVID- 19 pandemic.
- Three endpoints were moved from Secondary to Exploratory.
- Inclusion criterion no. 5 was revised to allow enrollment of subjects with central subfield retinal thickness cut-off value on SD-OCT of ≥320 µm instead of ≥340 µm.
- The assessment schedule table was corrected according to protocol body text and adjustment of appearance for clarity.

The conduct of the study is thus considered acceptable. No major concern may question the validity of the study. However, the Applicant was asked to further comment the impact of the revision of the inclusion criterion number 5 on central subfield retinal thickness (i.e. cut-off value on SD-OCT of ≥ 320 μm instead of ≥340 μm) on the efficacy results. The Applicant has provided a sensitivity analysis was performed for KESTREL and KITE on the subset of subjects with CSFT ≥340 µm. Results does not suggest that increased the cut-off from 320 to 340 µm had a significant impact on the results. Additionally, it is acknowledged that a 340 µm threshold makes the study population more representative of the real life.

Baseline data

Table 3: Demographic characteristics – Study B2301 and Study B2302 (FAS)

	Study B2301				Study B2302		
Characteristic	**Brolucizumab 3mg N=190**	**Brolucizumab 6mg N=189**	**Aflibercept 2mg N=187**	**Overall N=566**	**Brolucizumab 6mg N=179**	**Aflibercept 2mg N=181**	**Overall N=360**
Age group - n (%)							
< 65 years	97 (51.1)	104 (55.0)	93 (49.7)	294 (51.9)	100 (55.9)	102 (56.4)	202 (56.1)
>= 65 years	93 (48.9)	85 (45.0)	94 (50.3)	272 (48.1)	79 (44.1)	79 (43.6)	158 (43.9)
Age (years)							
n	190	189	187	566	179	181	360
Mean ± SD	64.4 ± 9.76	62.4 ± 10.14	63.9 ± 10.09	63.6 ± 10.01	62.3 ± 10.55	62.2 ± 9.48	62.2 ± 10.01
Min - Max	38 - 87	23 - 84	25 - 87	23 - 87	24 - 86	31 - 86	24 - 86
Median	64.0	64.0	65.0	64.0	64.0	63.0	63.0
Sex - n (%)							
Male	119 (62.6)	110 (58.2)	126 (67.4)	355 (62.7)	120 (67.0)	115 (63.5)	235 (65.3)
Female	71 (37.4)	79 (41.8)	61 (32.6)	211 (37.3)	59 (33.0)	66 (36.5)	125 (34.7)
Race - n (%)							
White	151 (79.5)	158 (83.6)	153 (81.8)	462 (81.6)	133 (74.3)	132 (72.9)	265 (73.6)
Black or African American	13 (6.8)	4 (2.1)	7 (3.7)	24 (4.2)	3 (1.7)	1 (0.6)	4 (1.1)
Asian	25 (13.2)	25 (13.2)	27 (14.4)	77 (13.6)	43 (24.0)	48 (26.5)	91 (25.3)
Chinese	2 (1.1)	0	1 (0.5)	3 (0.5)	13 (7.3)	17 (9.4)	30 (8.3)
Indian	3 (1.6)	5 (2.6)	2 (1.1)	10 (1.8)	14 (7.8)	11 (6.1)	25 (6.9)
Japanese	20 (10.5)	20 (10.6)	22 (11.8)	62 (11.0)	0	0	0
Korean	0	0	0	0	9 (5.0)	10 (5.5)	19 (5.3)
Vietnamese	0	0	0	0	0	1 (0.6)	1 (0.3)
Native Hawaiian or Other Pacific Islander	0	2 (1.1)	0	2 (0.4)	0	0	0
American Indian or Alaska Native	1 (0.5)	0	1 (0.5)	2 (0.4)	0	0	0
Ethnicity - n (%)							
Hispanic or Latino	50 (26.3)	61 (32.3)	55 (29.4)	166 (29.3)	3 (1.7)	4 (2.2)	7 (1.9)
Not Hispanic or Latino	133 (70.0)	118 (62.4)	129 (69.0)	380 (67.1)	163 (91.1)	170 (93.9)	333 (92.5)
Not reported	1 (0.5)	4 (2.1)	1 (0.5)	6 (1.1)	8 (4.5)	4 (2.2)	12 (3.3)
Unknown	6 (3.2)	6 (3.2)	2 (1.1)	14 (2.5)	5 (2.8)	3 (1.7)	8 (2.2)
Japanese ancestry*							
Yes	20 (10.5)	19 (10.1)	22 (11.8)	61 (10.8)			
No	170 (89.5)	170 (89.9)	165 (88.2)	505 (89.2)			

A subject can have multiple races.
* Only first or second generation
- Source: [Study B2301 Wk52-Table 10-5] and [Study B2302 Wk52-Table 10-5]

Table 4: Diabetes characteristics at baseline – Study B2301 and Study B2302 (FAS)

	Study B2301				Study B302		
Baseline Characteristics	**Brolucizumab 3mg N=190**	**Brolucizumab 6mg N=189**	**Aflibercept 2mg N=187**	**Overall N=566**	**Brolucizumab 6mg N=179**	**Aflibercept 2mg N=181**	**Overall N=360**
Diabetes type - m (%)							
n	190	189	187	566	179	181	360
Type I	10 (5.3)	12 (6.3)	6 (3.2)	28 (4.9)	19 (10.6)	7 (3.9)	26 (7.2)
Type II	180 (94.7)	177 (93.7)	181 (96.8)	538 (95.1)	160 (89.4)	174 (96.1)	334 (92.8)
HbA1c							
n	190	188	187	565	179	181	360
Mean ± SD	7.52 ± 1.160	7.69 ± 1.067	7.44 ± 1.132	7.55 ± 1.123	7.55 ± 1.174	7.46 ± 1.161	7.50 ± 1.166
Min - Max	4.7 – 9.9	5.0 – 10.0	4.3 – 10.2	4.3 – 10.2	5.0 – 10.0	5.2 – 10.0	5.0 – 10.0
Median	7.40	7.70	7.30	7.40	7.60	7.30	7.50
HbA1c group - m (%)							
< 7.5 %	100 (52.6)	76 (40.4)	107 (57.2)	283 (50.1)	82 (45.8)	96 (53.0)	178 (49.4)
>= 7.5 %	90 (47.4)	112 (59.6)	80 (42.8)	282 (49.9)	97 (54.2)	85 (47.0)	182 (50.6)

- n = number of subjects with an assessment.
- m = number of subjects with assessment meeting the criterion for the given categorical variables.
- Percentages (%) are calculated based on n.
- Diabetes type is based on primary diagnosis.
- Source: [Study B2301 Wk52-Table 10-6] and [Study B2302 Wk52-Table 10-6]

Table 5: Baseline ocular characteristics for the study eye – Study B2301 and Study B2302 (FAS)

	Study B2301				Study B2302		
Baseline Characteristics	**Brolucizumab 3mg N=190**	**Brolucizumab 6mg N=189**	**Aflibercept 2mg N=187**	**Overall N=566**	**Brolucizumab 6mg N=179**	**Aflibercept 2mg N=181**	**Overall N=360**
DME present – m (%)	190 (100)	189 (100)	187 (100)	566 (100)	179 (100)	181 (100)	360 (100)
Study eye – m (%)							
n	190	189	187	566	179	181	360
OS	97 (51.1)	98 (51.9)	95 (50.8)	290 (51.2)	95 (53.1)	97 (53.6)	192 (53.3)
OD	93 (48.9)	91 (48.1)	92 (49.2)	276 (48.8)	84 (46.9)	84 (46.4)	168 (46.7)
Time since DME diagnosis (months)							
n	190	189	187	566	179	181	360
Mean ± SD	12.5 ± 30.82	9.4 ± 19.47	9.6 ± 24.17	10.5 ± 25.26	10.4 ± 16.56	9.9 ± 20.73	10.2 ± 18.75
Min - Max	0 - 295	0 - 116	0 - 238	0 - 295	0 - 99	0 - 180	0 - 180
Median	2.0	1.8	1.8	1.9	3.6	2.9	3.2
Time since DME diagnosis group – m (%)							
n	190	189	187	566	179	181	360
<= 3 months	114 (60.0)	120 (63.5)	110 (58.8)	344 (60.8)	85 (47.5)	92 (50.8)	177 (49.2)
> 3 - < 12 months	34 (17.9)	30 (15.9)	39 (20.9)	103 (18.2)	51 (28.5)	49 (27.1)	100 (27.8)
>= 12 months	42 (22.1)	39 (20.6)	38 (20.3)	119 (21.0)	43 (24.0)	40 (22.1)	83 (23.1)
BCVA (letters)							
n	190	189	187	566	179	181	360
Mean ± SD	65.7 ± 11.09	66.6 ± 9.67	65.2 ± 12.38	65.8 ± 11.10	66.0 ± 10.77	63.7 ± 11.70	64.9 ± 11.29
Min - Max	28 - 78	30 - 78	23 - 79	23 - 79	23 - 78	25 - 92	23 - 92
Median	69.0	69.0	69.0	69.0	70.0	65.0	68.0

	Study B2301				Study B2302		
Baseline Characteristics	**Brolucizumab 3mg N=190**	**Brolucizumab 6mg N=189**	**Aflibercept 2mg N=187**	**Overall N=566**	**Brolucizumab 6mg N=179**	**Aflibercept 2mg N=181**	**Overall N=360**
BCVA group – m (%)							
n	190	189	187	566	179	181	360
<= 65 letters	78 (41.1)	74 (39.2)	64 (34.2)	216 (38.2)	65 (36.3)	91 (50.3)	156 (43.3)
> 65 letters	112 (58.9)	115 (60.8)	123 (65.8)	350 (61.8)	114 (63.7)	90 (49.7)	204 (56.7)
BCVA group – m (%)							
n	190	189	187	566	179	181	360
< 60 letters	44 (23.2)	36 (19.0)	41 (21.9)	121 (21.4)	42 (23.5)	50 (27.6)	92 (25.6)
>= 60 - <= 70 letters	68 (35.8)	70 (37.0)	71 (38.0)	209 (36.9)	55 (30.7)	73 (40.3)	128 (35.6)
> 70 letters	78 (41.1)	83 (43.9)	75 (40.1)	236 (41.7)	82 (45.8)	58 (32.0)	140 (38.9)
Macular Edema Type – m (%)							
n	188	186	182	556	178	175	353
Focal	61 (32.4)	59 (31.7)	48 (26.4)	168 (30.2)	63 (35.4)	66 (37.7)	129 (36.5)
Diffuse	127 (67.6)	127 (68.3)	134 (73.6)	388 (69.8)	115 (64.6)	109 (62.3)	224 (63.5)
Can't grade	0	0	0	0	0	0	0
N/A	0	0	0	0	0	0	0
CSFT (µm)							
n	190	189	187	566	179	180	359
Mean ± SD	456.0 ± 118.04	453.1 ± 123.42	475.6 ± 135.84	461.5 ± 126.11	481.1 ± 132.46	484.4 ± 134.58	482.7 ± 133.35
Min - Max	254 - 929	272 - 1023	258 - 1137	254 - 1137	299 - 992	264 - 1178	264 - 1178
Median	421.5	428.0	448.0	433.0	455.0	461.0	456.0
CSFT group – m (%)							
n	190	189	187	566	179	180	359
< 450 µm	111 (58.4)	107 (56.6)	96 (51.3)	314 (55.5)	85 (47.5)	82 (45.6)	167 (46.5)

	Study B2301				Study B2302		
Baseline Characteristics	**Brolucizumab 3mg N=190**	**Brolucizumab 6mg N=189**	**Aflibercept 2mg N=187**	**Overall N=566**	**Brolucizumab 6mg N=179**	**Aflibercept 2mg N=181**	**Overall N=360**
>= 450 - < 650 µm	64 (33.7)	70 (37.0)	71 (38.0)	205 (36.2)	74 (41.3)	79 (43.9)	153 (42.6)
>= 650 µm	15 (7.9)	12 (6.3)	20 (10.7)	47 (8.3)	20 (11.2)	19 (10.6)	39 (10.9)
Leakage on Fluorescein Angiography – m (%)							
n	188	186	182	556	178	175	353
Present	188 (100)	186 (100)	182 (100)	556 (100)	178 (100)	175 (100)	353 (100)
Absent	0	0	0	0	0	0	0
Intraretinal fluid – m (%)							
n	190	189	187	566	179	181	360
Present	190 (100)	189 (100)	184 (98.4)	563 (99.5)	176 (98.3)	179 (98.9)	355 (98.6)
Absent	0	0	3 (1.6)	3 (0.5)	3 (1.7)	2 (1.1)	5 (1.4)
Subretinal fluid – m (%)							
n	190	189	187	566	179	181	360
Present	60 (31.6)	62 (32.8)	61 (32.6)	183 (32.3)	56 (31.3)	67 (37.0)	123 (34.2)
Absent	130 (68.4)	127 (67.2)	126 (67.4)	383 (67.7)	123 (68.7)	114 (63.0)	237 (65.8)
Diabetic Retinopathy Severity Scale – m (%)							
n	185	186	184	555	176	177	353
1- DR absent	1 (0.5)	0	0	1 (0.2)	3 (1.7)	1 (0.6)	4 (1.1)
2- Microaneurysms only	3 (1.6)	1 (0.5)	3 (1.6)	7 (1.3)	0	2 (1.1)	2 (0.6)
3- Mild NPDR	56 (30.3)	57 (30.6)	52 (28.3)	165 (29.7)	49 (27.8)	37 (20.9)	86 (24.4)
4- Moderate NPDR	51 (27.6)	54 (29.0)	59 (32.1)	164 (29.5)	55 (31.3)	68 (38.4)	123 (34.8)

	Study B2301				Study B2302		
Baseline Characteristics	**Brolucizumab 3mg N=190**	**Brolucizumab 6mg N=189**	**Aflibercept 2mg N=187**	**Overall N=566**	**Brolucizumab 6mg N=179**	**Aflibercept 2mg N=181**	**Overall N=360**
5- Moderately severe NPDR	25 (13.5)	15 (8.1)	16 (8.7)	56 (10.1)	30 (17.0)	20 (11.3)	50 (14.2)
6- Severe NPDR	39 (21.1)	45 (24.2)	40 (21.7)	124 (22.3)	26 (14.8)	34 (19.2)	60 (17.0)
7- Mild PDR	6 (3.2)	3 (1.6)	7 (3.8)	16 (2.9)	9 (5.1)	7 (4.0)	16 (4.5)
8- Moderate PDR	4 (2.2)	8 (4.3)	5 (2.7)	17 (3.1)	3 (1.7)	5 (2.8)	8 (2.3)
9- High-Risk PDR	0	3 (1.6)	2 (1.1)	5 (0.9)	1 (0.6)	2 (1.1)	3 (0.8)
10- Very high-Risk PDR	0	0	0	0	0	0	0
11- Advanced PDR	0	0	0	0	0	1 (0.6)	1 (0.3)
12- Very advanced PDR	0	0	0	0	0	0	0

- n = number of subjects with an assessment.
- m = number of subjects with assessment meeting the criterion for the given categorical variables.
- Percentages (%) are calculated based on n.
- Source: [Study B2301 Wk52-Table 10-7] and [Study B2302 Wk52-Table 10-7]

There were no concerns about the balance of the demographics.

Regarding diabetes condition, the overall proportion of patients with type I diabetes remains very limited, 4.9 % in B2301 study and 7.2% B2302 study. As indicated by The Applicant, the proportion of Type I diabetes in KESTREL and KITE studies is consistent with the other anti-VEGF studies in DME population, which can be accepted. No discrepancies were observed in subgroup analysis

Overall, disease characteristics were well balanced among groups. However, we can observe a significant imbalance in the proportion of patients with a BCVA superior to 65 letters across groups in the B2302 study. The proportion was numerically higher in the brolucizumab group, 63.7%, than in the aflibercept group, 49.7%. Subpopulation analysis will be thus of importance to observe if results are not drive by this imbalance. The mean BCVA at baseline was 65.9 letters and 64.9 letters respectively in B2301 study and B2302 study.

Mean CSFT was 461.5 µm and 482.7 µm respectively in B2301 study and B2302 study with no critical discrepancies between arms. Macular Edema Type was mostly diffuse (69.8% and 63.5% respectively in B2301 study and B2302 study) and well balanced. Presence of intraretinal and presence of subretinal fluid were also balanced across study groups.

The time since diagnosis of DME was well balanced among groups, large majority of the patients having a diagnosis inferior to 3 months.

As clarified by the Applicant during the procedure, there have been only treatment-naïve subjects enrolled in KESTREL and KITE, i.e. subjects previously treated with anti-VEGF drugs or investigational drugs in the study eye were excluded.

Numbers analysed

B2301 Study

The proportion of subjects included in each analysis set by treatment arm is presented in the below table.

Table 6: Analysis sets (Randomized Set)

Analysis Population	Brolucizumab 3 mg n (%)	Brolucizumab 6 mg n (%)	Aflibercept 2 mg n (%)	Overall n (%)
Randomized set (RAN)	190 (100)	189 (100)	187 (100)	566 (100)
Full analysis set (FAS)	190 (100)	189 (100)	187 (100)	566 (100)
Safety set (SAF)	190 (100)	189 (100)	187 (100)	566 (100)
Per-protocol set (PPS)	142 (74.7)	152 (80.4)	145 (77.5)	439 (77.6)

Percentages (%) are based on "n" from Randomized Set.
Source: Table 14.1-2.1

B2302 Study

The proportion of subjects included in each analysis set by treatment arm is presented in the below table.

Table 7: Analysis sets (Randomized Set)

Analysis Population	Brolucizumab 6 mg n (%)	Aflibercept 2 mg n (%)	Overall n (%)
Randomized set (RAN)	179 (100)	181 (100)	360 (100)
Full analysis set (FAS)	179 (100)	181 (100)	360 (100)
Safety set (SAF)	179 (100)	181 (100)	360 (100)
Per-protocol set (PPS)	143 (79.9)	137 (75.7)	280 (77.8)

Percentages (%) are based on "n" from Randomized Set.
Source: Table 14.1-2.1

Outcomes and estimation

Primary endpoint

- ***Change from baseline in BCVA at Week 52***

Both Study B2301 and Study B2302 met the primary objective and confirmed the non-inferiority of brolucizumab 6 mg to aflibercept 2 mg for the primary endpoint, BCVA change from Baseline at Week 52 in the study eye, with a non-inferiority margin of 4 letters ($p<0.001$). The non-inferiority was not met for brolucizumab 3 mg.

In B2301, the LS mean estimate of change from baseline in BCVA at Week 52 was +9.2 letters in the brolucizumab 6 mg arm and +10.5 letters in the aflibercept 2 mg arm, with an LS mean difference between brolucizumab and aflibercept of -1.3 letters for brolucizumab 3 mg (95% CI: [-2.9, 0.3]).

In B2302, the LS mean estimate of change from baseline in BCVA at Week 52 was +10.6 letters in the brolucizumab arm and +9.4 letters in the aflibercept arm, with a LS mean difference between brolucizumab and aflibercept of 1.2 letters for brolucizumab (95% CI: [-0.6, 3.1]).

Table 8: Best Corrected Visual Acuity (letters read): ANOVA results for change from baseline at Week 52 for the study eye (Full Analysis Set – LOCF)

	Study B2301				Study B2302	
	Brolucizumab 3mg N=190	**Brolucizumab 6mg N=189**	**Aflibercept 2mg N=187**		**Brolucizumab 6mg N=179**	**Aflibercept 2mg N=181**
LS mean estimate (brolucizumab 3 mg vs aflibercept 2 mg)						
LS mean (SE)	7.3 (0.66)		10.6 (0.67)			
95% CI for LS mean	(6.0, 8.6)		(9.2, 11.9)			
LS mean estimate (brolucizumab 6 mg vs aflibercept 2 mg)						
LS mean (SE)		9.2 (0.57)	10.5 (0.57)		10.6 (0.66)	9.4 (0.66)
95% CI for LS mean		(8.1, 10.3)	(9.4, 11.7)		(9.3, 11.9)	(8.1, 10.7)
LS mean difference (Brolucizumab - Aflibercept)						
Difference (SE)	-3.3 (0.94)	-1.3 (0.81)			1.2 (0.94)	
95% CI for treatment difference	(-5.1, -1.4)	(-2.9, 0.3)			(-0.6,3.1)	
p-value for non-inferiority (4-letter margin) (1-sided)	0.227	<0.001			<0.001	

- Analyzed using ANOVA model with baseline BCVA categories (<=65, >65 letters), age categories (<65, >=65 years) and treatment as fixed effect factors.
- BCVA assessments after start of alternative DME treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment.
- Source: [Study B2301 Wk52-Table 11-1] and [Study B2302 Wk52-Table 11-1]

Sensitivity analysis

The change from baseline in BCVA at Week 52 for the study eye was analyzed using the FAS and a MMRM assuming missing at random and using observed data only to assess robustness of the hypothesis testing results. This analysis replaced the LOCF method for imputation/replacement of missing/censored BCVA data, which assumes no change after the start of monotone missing data, with MMRM, which assumes missing at random.

In Study B2301, non-inferiority of brolucizumab 6 mg to aflibercept 2 mg for the change from baseline in BCVA at Week 52 for the study eye using the MMRM was confirmed with a lower bound of the 95% CI for treatment difference above -4 letters (LS mean difference was -1.1 letters with 95% CI: [-2.7, 0.5]). Non-inferiority of brolucizumab 3 mg to aflibercept 2 mg was not achieved for the change from baseline in BCVA at Week 52 (95% CI: [-5.1, -1.3]).

In Study B2302, non-inferiority of brolucizumab 6 mg to aflibercept 2 mg for the change from baseline in BCVA at Week 52 for the study eye using MMRM was confirmed with a lower bound of the 95% CI for treatment difference above -4 letters (LS mean difference was 1.7 letters with 95% CI: [-0.0, 3.4]).

Per Protocol analysis

In Study B2301, in the brolucizumab 6 mg arm, non-inferiority of brolucizumab to aflibercept for the primary endpoint was confirmed in the PPS with a lower bound of the 95% CI for treatment difference above -4 letters (95% CI: [-3.2, 0.2]). In the brolucizumab 3 mg arm, non-inferiority of brolucizumab to aflibercept for the primary endpoint was not achieved in the PPS (95% CI: [-5.8, -1.6]).

Table 9: BCVA (letters read): ANOVA results for change from baseline at Week 52 for the study eye (PPS – LOCF) in Study B2301

	Brolucizumab 3 mg N=142	Brolucizumab 6 mg N=152	Aflibercept 2 mg N=145
Pairwise ANOVA			
n	142	152	145
LS mean estimate (Brolucizumab 3 mg vs. Aflibercept 2 mg)			
LS mean (SE)	7.8 (0.77)		11.5 (0.76)
95% CI for LS mean	(6.3, 9.3)		(10.0, 13.0)
LS mean estimate (Brolucizumab 6 mg vs. Aflibercept 2 mg)			
LS mean (SE)		9.8 (0.61)	11.4 (0.62)
95% CI for LS mean		(8.7, 11.0)	(10.1, 12.6)
LS mean difference (Brolucizumab - Aflibercept)			
Difference (SE)	-3.7 (1.08)	-1.5 (0.87)	
95% CI for treatment difference	(-5.8, -1.6)	(-3.2, 0.2)	

n is the number of subjects with data used in the model.
Analyzed using ANOVA model with baseline BCVA categories (≤65, >65 letters), age categories (<65, ≥65 years) and treatment as fixed effect factors.
BCVA assessments after start of alternative DME treatment in the study eye and/or use of prohibited medication/procedure are censored and replaced by the last value prior to start of this alternative treatment or prohibited medication/procedure.
Source: Table 14.2-1.3

In Study B2302, non-inferiority of brolucizumab 6 mg to aflibercept 2 mg for primary endpoint was confirmed in the PPS with a lower bound of the 95% CI for treatment difference above -4 letters.

Table 10: BCVA (letters read): ANOVA results for change from baseline at Week 52 for the study eye (PPS – LOCF) in Study B2302

	Brolucizumab 6 mg N=143	Aflibercept 2 mg N=137
LS mean estimate		
n	143	137
LS mean (SE)	12.0 (0.57)	10.7 (0.58)
95% CI for LS mean	(10.9, 13.2)	(9.6, 11.9)
LS mean difference (Brolucizumab - Aflibercept)		
Difference (SE)	1.3 (0.82)	
95% CI for treatment difference	(-0.3, 2.9)	

n is the number of subjects with data used in the model.
Analyzed using ANOVA model with baseline BCVA categories (<=65, >65 letters), age categories (<65, >=65 years) and treatment as fixed effect factors.
BCVA assessments after start of alternative DME treatment in the study eye and/or use of prohibited medication/procedure are censored and replaced by the last value prior to start of this alternative treatment or prohibited medication/procedure.
Source: Table 14.2-1.3

Impact of COVID-19 on the primary endpoint

The impact of COVID-19 on the change from baseline in BCVA at Week 52 for the study eye was analyzed by subgroup of COVID-19 exposure and impact using the same model and analysis strategy described for the primary endpoint. The results in the COVID-19 exposed/non-exposed and impacted/non-impacted subgroups were generally comparable with those of the overall population.

Key secondary endpoints

- ***Average change from baseline in BCVA over the period Week 40 through Week 52 (including in the testing strategy)***

Results for both studies are presented below.

Table 11: Best Corrected Visual Acuity (letters read): ANOVA results for average change from baseline over the period Week 40 through Week 52 for the study eye (Full Analysis Set – LOCF)

	Study B2301				Study B2302	
	Brolucizumab 3mg N=190	Brolucizumab 6mg N=189	Aflibercept 2mg N=187		Brolucizumab 6mg N=179	Aflibercept 2mg N=181
LS mean estimate (brolucizumab 3 mg vs aflibercept 2 mg)						
LS mean (SE)	7.0 (0.63)		10.5 (0.64)			
95% CI for LS mean	(5.8, 8.3)		(9.2, 11.7)			
LS mean estimate (brolucizumab 6 mg vs aflibercept 2 mg)						
LS mean (SE)		9.0 (0.53)	10.5 (0.53)		10.3 (0.62)	9.4 (0.62)
95% CI for LS mean		(7.9, 10.0)	(9.4, 11.5)		(9.1, 11.5)	(8.2, 10.6)
LS mean difference (Brolucizumab - Aflibercept)						
Difference (SE)	-3.5 (0.90)	-1.5 (0.75)			0.9 (0.88)	
95% CI for treatment difference	(-5.2, -1.7)	(-3.0, -0.0)			(-0.9, 2.6)	
p-value for non-inferiority (4-letter margin) (1-sided)		<0.001			<0.001	
p-value for superiority (1-sided)					0.164	
- Analyzed using ANOVA model with baseline BCVA categories (<=65, >65 letters), age categories (<65, >=65 years) and treatment as fixed effect factors. - BCVA assessments after start of alternative DME treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment. - Source: [Study B2301 Wk52-Table 11-3] and [Study B2302 Wk52-Table 11-3]						

B2301 Study

The study met its first key secondary objective, demonstrating non-inferiority of brolucizumab 6 mg to aflibercept 2 mg for the first key secondary endpoint.

This analsyis was not conducted for brolucizumab 3 mg considering that the primary analysis was not met.

The LS mean difference between brolucizumab 6 mg and aflibercept 2 mg arm was -1.5 letters for brolucizumab (95% CI: [-3.0, -0.0]). The LS mean difference between brolucizumab 3 mg and aflibercept 2 mg was -3.5 letters for brolucizumab (95% CI: [-5.2, -1.7]).

A superiority hypothesis test was planned to assess the average change from baseline in BCVA over the period Week 40 through Week 52. However, since non-inferiority for change from baseline in BCVA at Week 52 for brolucizumab 3 mg compared to aflibercept 2 mg was not achieved (p=0.227), and non-inferiority of brolucizumab 3 mg to aflibercept 2 mg was not tested for the average change from baseline in BCVA over the period Week 40 through Week 52, confirmatory testing did not proceed to assess superiority of brolucizumab 6 mg vs. aflibercept 2 mg for the average change from baseline in BCVA over the period Week 40 through Week 52.

B2302 Study

The study met its first key secondary objective, demonstrating non-inferiority of brolucizumab 6 mg to aflibercept 2 mg for the first key secondary endpoint average change from baseline in BCVA over the period Week 40 through Week 52 for the study eye, with a non-inferiority margin of 4 letters. The LS mean difference between the brolucizumab and aflibercept arms was 0.9 letters for brolucizumab (95% CI: [-0.9, 2.6]).

• Proportion of subjects maintaining q12w treatment status at Week 52 (not including in the testing strategy)

The DAAs (Disease Activity Assessments) were performed to identify q8w-need in each treatment arm at pre-specified visits during the first year of the study (Weeks 32, 36 and 48).

Subjects in the aflibercept 2 mg arm were on a two-month (q8w) dosing interval after the loading phase as per protocol, and were not allowed to switch on q12w regimen.

B2301 Study

In the brolucizumab 6 mg arm, the proportion of subjects maintained on a q12w regimen through year one (i.e., on a three-month dosing interval) was 55.1% (95% CI: [46.9, 62.5]). In the brolucizumab 3 mg arm, this proportion was 47.4% (95% CI: [39.3, 55.1]).

The majority of subjects with q8w-need in the brolucizumab arms were identified via DAA at the Week 32 and Week 36 visits (33 and 27 subjects, respectively, out of 71 subjects with q8w-need identified up to Week 52 in the brolucizumab 6 mg arm, and 40 and 32 subjects, respectively, out of 82 subjects with q8w-need identified up to Week 52 in the brolucizumab 3 mg arm), i.e., during the initial q12w cycle after the loading phase.

Within the 98 subjects in the brolucizumab 6 mg arm with no q8w-need identified during the initial q12w cycle (i.e., that qualified for q12w treatment at Week 36), 87.6% (95% CI: [78.8, 93.0]) remained on q12w at Week 52. Within the 82 subjects in the brolucizumab 3 mg arm with no q8w-need identified during the initial q12w cycle, 87.0% (95% CI: [77.2, 92.8]) remained on q12w at Week 52.

Table 12: Time-to-first q8w treatment need: summary for brolucizumab subjects by DAA visit (FAS – Efficacy/Safety approach)

Time (week)	Number of subjects with first q8w-need at visit	Number of subjects under risk at this visit	Number censored at the visit	Prob. of maintaining on q12w (survival)	95% CI for probability of maintaining on q12w
Brolucizumab 3 mg (N=190)					
0	0	190	25	1	NA, NA
32	40	165	11	0.758	0.685, 0.816
36	32	114	5	0.545	0.463, 0.619
48	10	77	0	0.474	0.393, 0.551
Brolucizumab 6 mg (N=189)					
0	0	189	23	1	NA, NA
32	33	166	8	0.801	0.732, 0.854
36	27	125	9	0.628	0.548, 0.698
48	11	89	0	0.551	0.469, 0.625

Censored: subjects are considered to no longer be under risk for a q8w-need identification at later visits.
Efficacy/Safety approach: censored data attributable to lack of efficacy and/or safety are imputed with q8w-need = Yes at the next DAA visit.
Source: Table 14.2-2.1

B2302 Study

The proportion of subjects maintained on a q12w regimen through year one 50.3% (95% CI: [42.5, 57.7]).

The majority of subjects with q8w-need in the brolucizumab arm were identified at the Week 32 and Week 36 visits (44 and 35 subjects, respectively, out of 83 subjects with q8w-need up to Week 52; Table 11-5), i.e., the two DAA visits of the initial q12w cycle after the loading phase. At the DAA visit at Week 48 only 4 additional subjects were identified as having q8w-need.

Within the 87 subjects with no q8w-need identified during the initial q12w cycle (i.e., that qualified for q12w treatment at Week 36), 95.1% (95% CI: [87.4, 98.1]) remained on q12w at Week 52 (Table 11-6; Figure 14.2-2.2).

Table 13: Time-to-first q8w treatment need: summary for brolucizumab subjects by DAA visit (FAS – Efficacy/Safety approach)

Brolucizumab 6 mg (N = 179)					
Time (week)	Number of subjects with first q8w-need at the visit	Number of subjects under q8w-need risk at the visit	Number censored at the visit	Prob. Of maintaining on q12w (survival)	95% CI for probability of maintaining on q12w
0	0	179	8	1	NA, NA
32	44	171	5	0.743	0.670, 0.802
36	35	122	6	0.530	0.451, 0.602
48	4	81	0	0.503	0.425, 0.577

Censored: subjects are considered to no longer be under risk for a q8w-need identification at later visits.
Efficacy/Safety approach: censored data attributable to lack of efficacy and/or safety are imputed with q8w-need = Yes at the next DAA visit.
Source: Table 14.2-2.1

Secondary endpoints to be analysed in a superiority testing (B2302 Study)

Only results for B2302 study are presented below, since non-inferiority for change from baseline in BCVA at Week 52 for brolucizumab 3 mg compared to aflibercept 2 mg was not achieved (p=0.227) in B2301. study.

- ***Average change from baseline in CSFT over the period Week 40 through Week 52***

B2302 Study

The LS mean of the change from baseline in CSFT showed a reduction in the brolucizumab arm (-187.1 µm) statistically superior (p=0.00) compared to the aflibercept arm (-157.7 µm), with an estimated difference of -29.4 µm (95% CI: [-48.6, -10.2]).

Table 14: CSFT (micrometer): ANOVA results for average change from baseline over the period Week 40 through Week 52 for the study eye (FAS – LOCF)

	Brolucizumab 6 mg N=179	Aflibercept 2 mg N=181
LS mean estimate		
n	179	180
LS mean (SE)	-187.1 (6.91)	-157.7 (6.89)
95% CI for LS mean	(-200.7, -173.5)	(-171.2, -144.1)
LS mean difference (Brolucizumab - Aflibercept)		
Difference (SE)	-29.4 (9.76)	
95% CI for treatment difference	(-48.6, -10.2)	
p-value for superiority (1-sided)	0.001	

n is the number of subjects with data used in the model.
Analyzed using ANOVA model with baseline CSFT categories (<450, >=450 - <650, >=650 µm), age categories (<65, >=65 years) and treatment as fixed effect factors.
CSFT assessments after start of alternative DME treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment.
Source: Table 14.2-5.3

- ***Average change from baseline in BCVA over the period Week 40 through Week 52 in the study eye***

B2302 Study

In addition of the non-inferiority testing from the first key secondary endpoint, superiority hypothesis test was also performed for the average change from baseline in BCVA over the period Week 40 through Week 52 but did not reach statistical significance (p=0.164; assessed at a one-sided significance level of 0.025).

24-months results from the KITE study

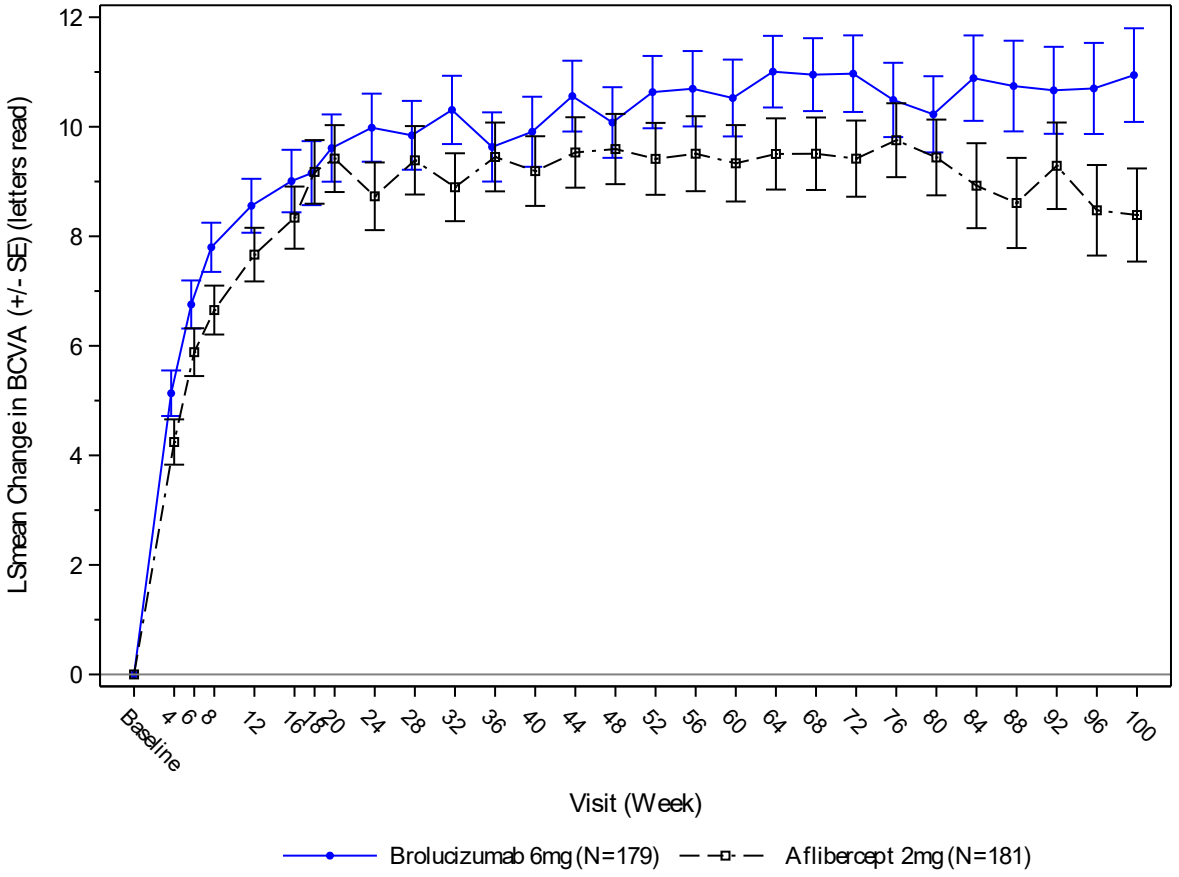
Further to a request by CHMP, the Applicant has submitted results up to week 100.

Sustained BCVA gain from baseline through Week 100

The LS mean change from baseline in BCVA at each visit from baseline up to Week 100 is presented in Figure 3-1. A rapid improvement of visual acuity was observed up to Week 32 in both treatment arms. This effect was maintained up to Week 100 with the observed LS mean change from baseline in BCVA at each visit showing numerically higher gains in the brolucizumab 6 mg arm compared to the aflibercept 2 mg arm at all post-baseline visits, except one (Week 18, where values were equal). Overall, the subjects in the brolucizumab 6 mg arm presented continued improvements in visual acuity during both the loading and maintenance phases. The LS mean estimate of change from baseline in BCVA at Week 100 was +10.9 letters in the brolucizumab 6 mg arm and +8.4 letters in the aflibercept 2 mg arm, with a LS mean difference between brolucizumab 6 mg and aflibercept 2 mg of 2.6 letters in favor of brolucizumab 6 mg (95% CI: [0.2, 4.9]; Table 3-1).

In KITE at Week 100, the proportion of subjects who gained ≥15 letters in BCVA from baseline or reached BCVA ≥84 letters for the study eye was 49.7% in the brolucizumab 6 mg arm compared to 37.6% in the aflibercept 2 mg arm, with a LS mean difference of 13.6% in favor of brolucizumab 6 mg arm (95% CI: [3.3, 23.5]; Table 3-2). In addition, the observed proportion of subjects who lost ≥15 letters in BCVA from baseline at Week 100 for the study eye was 2.2% in the brolucizumab 6 mg arm compared to 3.3% in the aflibercept 2 mg arm, with an estimated treatment difference of -1.3% in favor of brolucizumab 6 mg arm (95% CI: [-4.8, 2.0]; Table 3-2)

Figure 3-1 BCVA (letters read): line plot of LS mean change (+/- SE) from baseline by visit for the study eye in KITE (Full Analysis Set - LOCF)



- LS mean and SE estimates are based on an ANOVA model with baseline BCVA categories (<=65, >65 letters), age categories (<65, >=65 years) and treatment as fixed effect factors.
- BCVA assessments after start of alternative DME treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment.

Table 3-1BCVA (letters read): ANOVA results for change from baseline at Week 100 for the study eye in KITE (Full Analysis Set - LOCF)

	Brolucizumab 6mg N=179	Aflibercept 2mg N=181
LS mean estimate		
N	179	181
LS mean (SE)	10.9 (0.85)	8.4 (0.85)
95% CI for LS mean	(9.3, 12.6)	(6.7, 10.1)
LS mean difference (Brolucizumab - Aflibercept)		
Difference (SE)	2.6 (1.21)	
95% CI for treatment difference	(0.2, 4.9)	

- n is the number of subjects with data used in the model.
- Analyzed using ANOVA model with baseline BCVA categories (<=65, >65 letters), age categories (<65, >=65 years) and treatment as fixed effect factors.
- BCVA assessments after start of alternative DME treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment.

Table 3-2 BCVA (letters read): Number (%) of subjects with BCVA gain or loss for the study eye at Week 100 in KITE (FAS - LOCF)

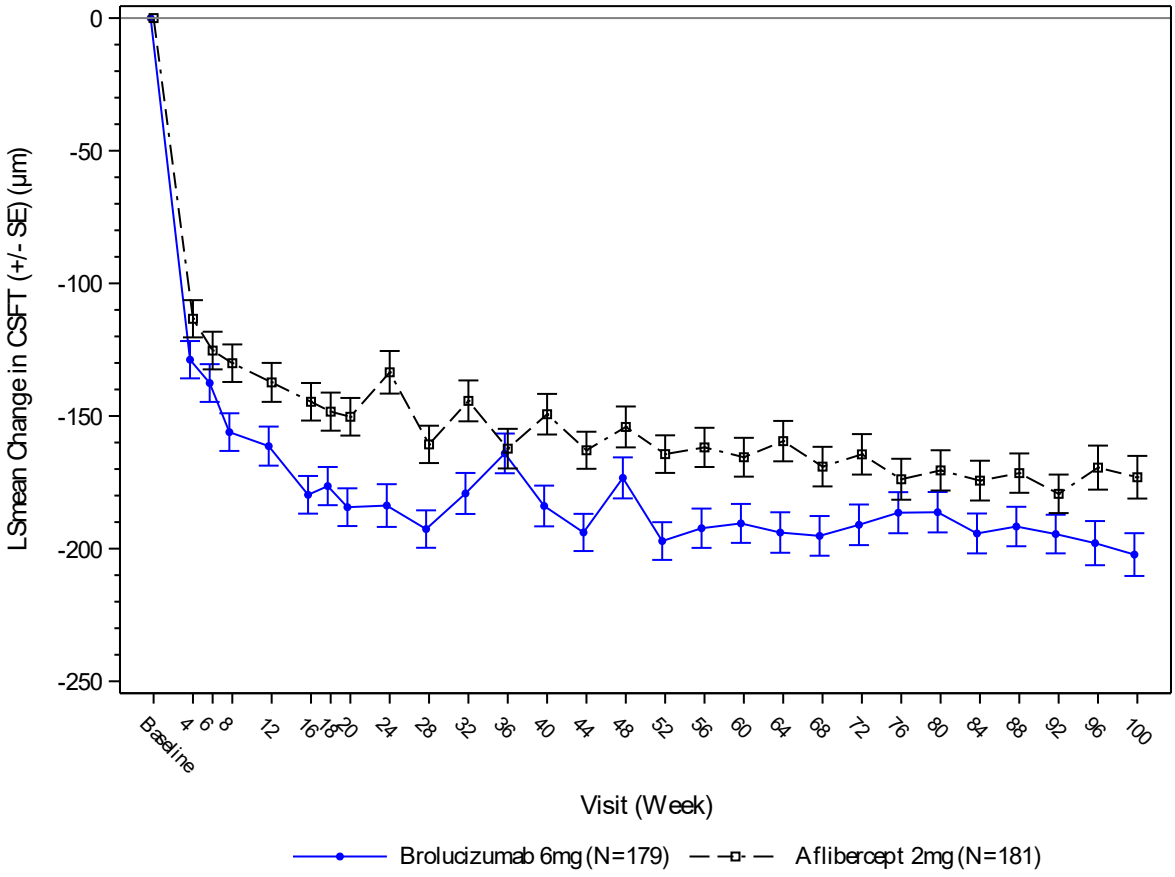
	Brolucizumab 6 mg N=179	Aflibercept 2 mg N=181
>= 15 letters gain from baseline or BCVA >=84 letters at Week 100		
Proportion of subjects - n/M (%)	89/179 (49.7)	68/181 (37.6)
95% CI [1]	(42.2, 57.3)	(30.5, 45.1)
Comparison of BRO vs AFL		
[2] Proportion estimates	50.4	36.9
Difference - %	13.6	
95% CI for treatment difference	(3.3, 23.5)	
>= 15 letters loss from baseline at Week 100	4/179 (2.2)	6/181 (3.3)
95% CI [1]	(0.6, 5.6)	(1.2, 7.1)
Comparison of BRO vs AFL		
[2] Proportion estimates	2.1	3.5
Difference - %	-1.3	
95% CI for treatment difference	(-4.8, 2.0)	

- n = number of subjects satisfying the criteria of the response variable.
- M = number of subjects with an assessment of the criterion.
- [1] 95% CI for binomial proportions is based on Clopper-Pearson exact method.
- [2] Statistical model used logistic regression adjusting for baseline BCVA categories (<=65, >65 letters), age categories (<65, >=65 years) and treatment as fixed effect factors. 95% CI for the treatment difference estimated using bootstrap method.
- BCVA assessments after start of alternative DME treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment.

Consistent anatomical improvement in CSFT reduction and IRF/SRF resolution from baseline through Week 100

In KITE, at almost all post-baseline visits through Week 100, anatomical improvement with numerically greater reduction in central subfield thickness from baseline (Figure 3-2) and a lower proportion of subjects with presence of retinal fluid (IRF and/or SRF) (Figure 3-3) was also observed for brolucizumab 6 mg compared to aflibercept 2 mg.

Figure 3-2 CSFT (micrometer): line plot of LS mean change (+/- SE) from baseline by visit for the study eye in KITE (Full Analysis Set - LOCF)



- LS mean and SE estimates are based on an ANOVA model with baseline CSFT categories (<450, >=450-<650, >=650 um), age categories (<65, >=65 years) and treatment as fixed effect factors.
- CSFT assessments after start of alternative DME treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment.

High proportion of subjects deemed suitable for q12w at Weeks 32/36 (first q12w cycle) remained on q12w/q16w through Week 100

The KITE 100-week data confirm the predictability of the effect observed during the first q12w cycle in year 1, since the majority of subjects (69.6%) who were suitable for a q12w regimen at Week 32 and Week 36 (based on the disease activity assessment by the masked investigator) were able to remain on a q12w/q16w regimen through Week 100 (year 2).

The proportion of subjects in the KITE brolucizumab 6 mg arm maintaining a q12w treatment regimen up to Week 64 (after three q12w treatment intervals following the loading phase) was 45.5% (95% CI: [37.7, 53.0]), and maintaining q12w/q16w up to Week 100 was 36.8% (95%

CI: [29.1, 44.5]; (Table 3-3). In addition, 87.9% (95% CI: [73.3, 94.8]) of the subjects on q12w at Week 68 and on q16w at Week 76, were maintained on q16w at Week 100.

Table 3-3 Time-to-first q8w treatment need: summary for brolucizumab subjects by DAA visit in KITE (FAS- Efficacy/Safety approach)

Brolucizumab 6 mg
N = 179

Time (wee	Number of subjects with first q8w-need at visit	Number of subjects under q8w-need risk at	Number censored at the	Prob. Of maintaining on q12w/q16w	95% CI for probability of maintaining
0	0	179	8	1	NA, NA
32	44	171	5	0.743	0.670, 0.802
36	35	122	6	0.530	0.451, 0.602
48	4	81	4	0.503	0.425, 0.577
60	7	73	4	0.455	0.377, 0.530
72	5	62	4	0.418	0.341, 0.494
76	2	53	4	0.403	0.325, 0.479
80	0	47	0	0.403	0.325, 0.479
84	1	47	0	0.394	0.317, 0.470
88	0	46	0	0.394	0.317, 0.470
92	3	46	1	0.368	0.291, 0.445
96	0	42	0	0.368	0.291, 0.445

- Censored: subjects are considered to no longer be under risk for a q8w-need identification at later visits.
- Efficacy/Safety approach: censored data attributable to lack of efficacy and/or safety are imputed with q8w- need = Yes at the next disease activity assessment visit.
- Subjects extended to q16w after Week 72 are included as no q8w-need.

For the 87 subjects in KITE who qualified for q12w treatment at Week 36 (at year 1), the year 2 results confirm that the majority of these subjects were maintained on q12w at Week 64 (85.9%, 95% CI: [76.0, 92.0]) and on q12w/q16w at Week 100 (69.6%, 95% CI: [57.4, 78.9],

Table 3-4). These data suggest that most subjects suitable for q12w treatment interval can be identified during the first q12w treatment cycle which occurs in year one and also the predictability of effect seen during the initial q12w cycle extends beyond the first year of treatment.

Table 3-4 Time-to-first q8w treatment need: summary for brolucizumab subjects by DAA visit within those subjects with no q8w-need during the initial q12w cycle in KITE (FAS - Efficacy/Safety approach)

Brolucizumab 6 mg
N = 87

Time (week)	Number of subjects with first q8w-need at visit	Number of subjects under q8w-need risk at this visit	Number censored at the visit	Prob. of maintaining on q12w/q16w (survival)	95% CI for probability of maintaining q12w/q16w
0	0	87	0	1	NA, NA
32	0	87	0	1	NA, NA
36	0	87	6	1	NA, NA
48	4	81	4	0.951	0.874, 0.981

Brolucizumab 6 mg N = 87					
Time (week)	**Number of subjects with first q8w- need at visit**	**Number of subjects under q8w-**	**Number censored at the visit**	**Prob. of maintaining on q12w/q16w (survival)**	**95% CI for probability of maintaining on q12w/q16w**
60	7	73	4	0.859	0.760, 0.920
72	5	62	4	0.790	0.680, 0.866
76	2	53	4	0.760	0.646, 0.842
80	0	47	0	0.760	0.646, 0.842
84	1	47	0	0.744	0.628, 0.829
88	0	46	0	0.744	0.628, 0.829
92	3	46	1	0.696	0.574, 0.789
96	0	42	0	0.696	0.574, 0.789

- Censored: subjects are considered to no longer be under risk for a q8w-need identification at later visits.
- Efficacy/Safety approach: censored data attributable to lack of efficacy and/or safety are imputed with q8w- need = Yes at the next disease activity assessment visit.
- Subjects extended to q16w after Week 72 are included as no q8w-need.

In KITE, a high proportion study treatment period were still on extended treatment regimens (q12w or q16w) at Week 100 (Table 3-5on of the subjects (47.5%) in the brolucizumab 6 mg arm from those who completed the 96-week). The remaining subjects in the brolucizumab arm (52.5%) were on q8w treatment regimen at the end of the study.

Table 3-5 Treatment status at Week 100 in KITE (FAS)

Treatment Status	Brolucizumab 6 mg N=179 n/M (%)
q8w	74/141 (52.5)
q12w	32/141 (22.7)
q16w	35/141 (24.8)

- n = number of subjects satisfying the condition.
- M = number of subjects who completed study treatment.

The treatment status at Week 100 within subjects with 4-week extension of treatment interval from previous regimen at Week 72 and Week 76 is presented in Table 3-6. The majority of subjects from those assigned to a 4-week extension of treatment interval at Week 72 and Week 76 were still on the assigned treatment regimens at Week 100: 54.5% of the subjects extended from q8w to q12w were on q12w treatment regimen and 83.3% of the subjects extended from q12w to q16w were on q16w at Week 100.

Table 3-6 Treatment status at Week 100 within subjects with 4-weeks extension of treatment interval from previous regimen at Week 72/76 in KITE (FAS)

Regimen extension at Week 72/76	Treatment status at Week 100	Brolucizumab 6 mg N=179 n/M (%)

q8w to q12w	q12w	24/ 44 (54.5)
	q8w	20/ 44 (45.5)
q12w to q16w	q16w	35/ 42 (83.3)
	q8w	7/ 42 (16.7)

- n = number of subjects satisfying the condition.
- M = number of subjects who completed study treatment under each category.

Overall, the results of KITE year 2 data demonstrate the sustained BCVA gain and anatomical improvement in brolucizumab 6 mg arm are maintained through Week 100. This observation confirms a 5xq6w loading dose of brolucizumab 6 mg, followed by an individualized treatment regimen in DME as q12w if no disease activity, or q8w if disease activity is identified during year 1 maintenance phase. In addition, if disease stability is observed, the dosing interval could be further extended up to q16w based on the treating physician's discretion. The individualized treatment regimen for the DME patient is determined by their response to the treatment and their disease control status as assessed by the treating physician. The high proportion (69.6%) of KITE subjects in the brolucizumab 6 mg arm who were identified as "no q8w treatment need" during the initial q12w cycle (at Weeks 32/36) and remained on q12w or q16w at Week 100 also supports the appropriateness of the q12w interval during the maintenance phase for DME patients.

The results overall support maintenance of the benefits over time and adequacy of the regimen proposed.

Ancillary analyses

Secondary endpoints initially planned in the SAP to be analysed in a superiority testing

In B2301 study, since non-inferiority for change from baseline in BCVA at Week 52 for brolucizumab 3 mg compared to aflibercept 2 mg was not achieved (p=0.227) and non-inferiority of brolucizumab 3 mg to aflibercept 2 mg was not tested for the average change from baseline in BCVA over the period Week 40 through Week 52, confirmatory testing did not proceed to assess superiority of brolucizumab 6 mg vs. aflibercept 2 mg for the average change from baseline in BCVA over the period Week 40 through Week 52, as well for the two following endpoints: average change from baseline in CSFT over the period Week 40 through Week 52 and Presence of subretinal fluid and intraretinal fluid at Week 52.

In B2301 study, since the non-in given that the superiority testing for the average change from baseline in BCVA over the period Week 40 through Week 52 did not reach statistical significance (p=0.164), the confirmatory testing of superiority was not performed for the proportion of subjects without SRF and IRF at Week 52.

However, the Applicant provided estimated differences across groups for these outcomes.

- ***Average change from baseline in CSFT over the period Week 40 through Week 52***

B2301 Study

The LS mean change from baseline in CSFT was -159.5 µm in the brolucizumab 6 mg arm and -158.1 µm in the aflibercept 2 mg arm, with an estimated difference of -1.4 µm (95% CI: [-17.9, 15.0]). The estimated difference between the brolucizumab 3 mg arm and the aflibercept 2 mg arm was 4.9 µm (95% CI: [-12.3, 22.1]).

Table 15: CSFT (micrometers): ANOVA results for average change from baseline over the period Week 40 through Week 52 for the study eye (FAS – LOCF)

CHMP assessment report
EMA/23630/2020 Page 52/125

	Brolucizumab 3 mg N=190	Brolucizumab 6 mg N=189	Aflibercept 2 mg N=187
Pairwise ANOVA			
N	190	189	187
LS mean estimate (Brolucizumab 3 mg vs. Aflibercept 2 mg)			
LS mean (SE)	-153.0 (6.14)		-157.9 (6.19)
95% CI for LS mean	(-165.0, -140.9)		(-170.1, -145.7)
LS mean estimate (Brolucizumab 6 mg vs. Aflibercept 2 mg)			
LS mean (SE)		-159.5 (5.88)	-158.1 (5.91)
95% CI for LS mean		(-171.1, -148.0)	(-169.7, -146.5)
LS mean difference (Brolucizumab - Aflibercept)			
Difference (SE)	4.9 (8.74)	-1.4 (8.36)	
95% CI for treatment difference	(-12.3, 22.1)	(-17.9, 15.0)	

n is the number of subjects with data used in the model.
Analyzed using ANOVA model with baseline CSFT categories (<450, ≥450 - <650, ≥650 µm), age categories (<65, ≥65 years) and treatment as fixed effect factors.
CSFT assessments after start of alternative DME treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment.
Source: Table 14.2-5.3

- ***Presence of subretinal fluid and intraretinal fluid (central subfield) at Week 52***

B2301 Study

Estimated differences between brolucizumab and aflibercept were -13.2% (95% CI: [-23.2, -3.8]) in favor of brolucizumab 6 mg and -14.1% (95% CI: [-23.3, -4.6]) in favor of brolucizumab 3 mg

Table 16: SRF and IRF status in the central subfield: Proportion of subjects with presence of SRF and/or IRF in the study eye at Week 52 (FAS – LOCF)

	Brolucizumab 3 mg N=190	Brolucizumab 6 mg N=189	Aflibercept 2 mg N=187
Proportion of subjects - n/M (%)	113/190 (59.5)	114/189 (60.3)	137/187 (73.3)
95% CI [1]	(52.1, 66.5)	(53.0, 67.3)	(66.3, 79.5)
Comparison of Brolucizumab 3 mg vs. Aflibercept 2 mg [2]			
Proportion estimates (%)	59.5		73.6
Difference - %	-14.1		
95% CI for treatment difference	(-23.3, -4.6)		
Comparison of Brolucizumab 6 mg vs. Aflibercept 2 mg [2]			
Proportion estimates (%)		60.4	73.5
Difference - %		-13.2	
95% CI for treatment difference		(-23.2, -3.8)	

n = number of subjects satisfying the criteria of the response variable.
M = number of subjects with an assessment of the criterion.
[1] 95% CI for binomial proportions is based on Clopper-Pearson exact method.
[2] Statistical model used logistic regression adjusting for baseline fluid status (SRF and/or IRF), age categories (<65, ≥65 years) and treatment as fixed effect factors.
95% CI for the treatment difference estimated using bootstrap method.
Fluid status assessments after start of alternative DME treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment.
Source: Table 14.2-6.3

B2302 Study

Lower proportion of subjects with presence of SRF and/or IRF in the study eye at Week 52 were observed in the brolucizumab arm (54.2%) compared to the aflibercept arm (72.9%), with an estimated difference of -18.4% (95% CI: [-28.5, -8.3]).

Table 17: SRF and IRF status in the central subfield: proportion of subjects with presence of SRF and/or IRF in the study eye at Week 52 (FAS – LOCF)

CHMP assessment report
EMA/23630/2020 Page 53/125

	Brolucizumab 6 mg N=179	Aflibercept 2 mg N=181
Proportion of subjects - n/M (%)	97/179 (54.2)	132/181 (72.9)
95% CI [1]	(46.6, 61.6)	(65.8, 79.3)
Comparison of Brolucizumab vs. Aflibercept [2]		
Proportion estimates (%)	54.5	72.9
Difference - %	-18.4	
95% CI for treatment difference	(-28.5, -8.3)	

n = number of subjects satisfying the criteria of the response variable.
M = number of subjects with an assessment of the criterion.
[1] 95% CI for binomial proportions is based on Clopper-Pearson exact method.
[2] Statistical model used logistic regression adjusting for baseline fluid status (SRF and/or IRF), age categories (<65, >=65 years) and treatment as fixed effect factors.
95% CI for the treatment difference estimated using bootstrap method.
Fluid status assessments after start of alternative DME treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment.
Source: Table 14.2-6.3

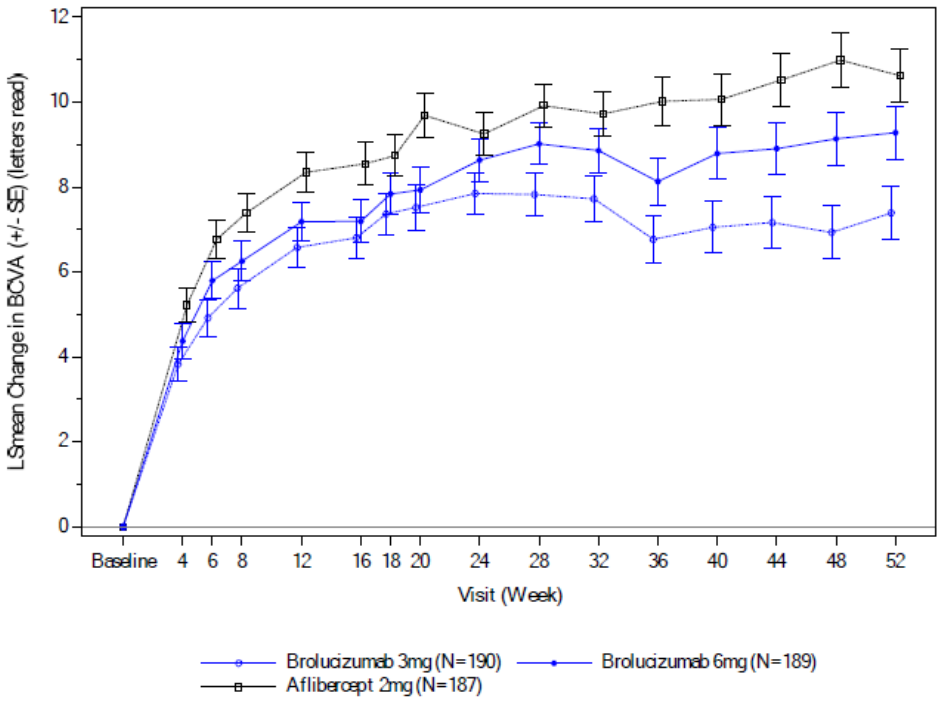
Secondary endpoints (Not included in the testing hierarchy)

- ***Change from baseline in BCVA to each post-baseline visit up to Week 52***

B2301 Study

The maximum observed difference in change from baseline in BCVA between the brolucizumab 6 mg arm and the aflibercept 2 mg arm up to Week 52 was -1.9 letters (95% CI: [-3.5, -0.3]) at Week 36. The maximum observed difference between the brolucizumab 3 mg and the aflibercept 2 mg arm was -4.1 letters (95% CI: [-6.0, -2.2]) at Week 48.

Figure 3. BCVA (letters read): line plot of LS mean change (+/- SE) from baseline by visit for the study eye (FAS – LOCF)



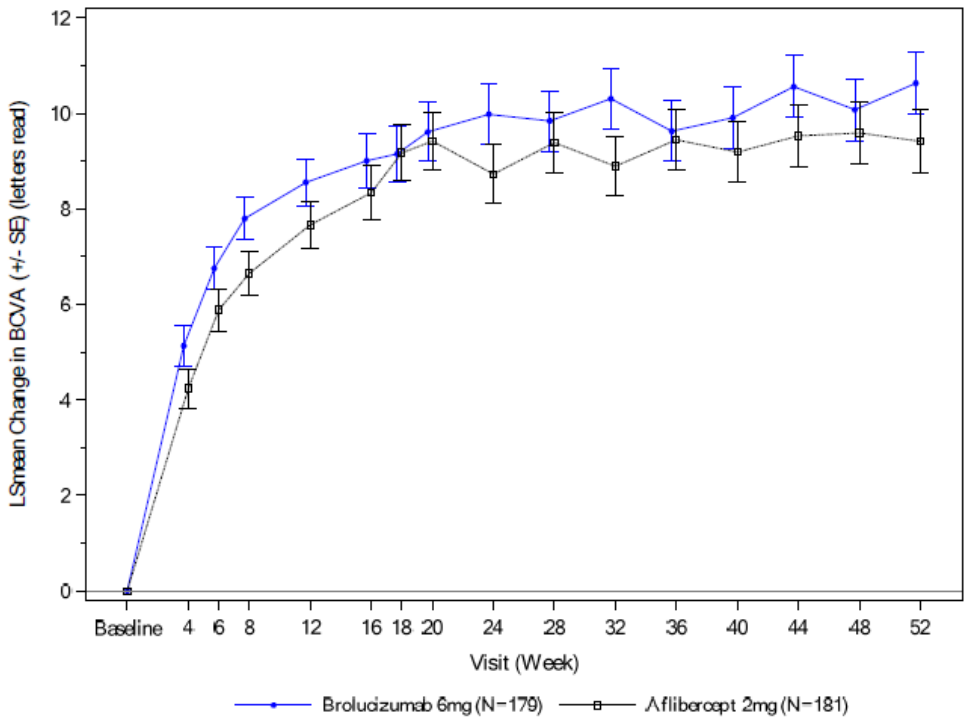
LS mean and SE estimates are based on an ANOVA model with baseline BCVA categories (≤65, >65 letters), age categories (<65, ≥65 years) and treatment as fixed effect factors.
BCVA assessments after start of alternative DME treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment.
Source: Table 14.2-3.5

CHMP assessment report
EMA/23630/2020 Page 54/125

B2302 Study

The observed LS mean change from baseline in BCVA at each visit showed numerically higher gains in the brolucizumab arm compared to the aflibercept arm at all post-baseline visits except one (Week 18, where values were equal) up to Week 52, there were no clinically relevant differences observed between the treatment arms.

Figure 4. BCVA (letters read): line plot of LS mean change (+/- SE) from baseline by visit for the study eye (FAS – LOCF)



LS mean and SE estimates are based on an ANOVA model with baseline BCVA categories (<=65, >65 letters), age categories (<65, >=65 years) and treatment as fixed effect factors.
BCVA assessments after start of alternative DME treatment in the study eye are censored and replaced by the last value prior to the start of this alternative treatment.
Source: Table 14.2-3.5

- ***Proportion of subjects with BCVA gain of >=5, >=10 and >=15 ETDRS letters from baseline***

B2301 Study

Table 18: Gain in BCVA (letters read): number (%) of subjects who gained >= 5, 10, or 15 letters in BCVA from baseline or reached BCVA >= 84 letters at Week 52 for the study eye (FAS – LOCF)

CHMP assessment report
EMA/23630/2020 Page 55/125

Secondary endpoint	BRO 3 mg n/M (%)	BRO 6 mg n/M (%)	AFL 2 mg n/M (%)	Difference (95% CI) [1]
≥5 letters gain from baseline or BCVA ≥84 letters at Week 52	127/190 (66.8)	142/189 (75.1)	145/187 (77.5)	BRO 3 mg – AFL 2 mg -11.7 (-20.6, -2.8) BRO 6 mg – AFL 2 mg -3.5 (-11.9, 5.3)
≥10 letters gain from baseline or BCVA ≥84 letters at Week 52	90/190 (47.4)	100/189 (52.9)	106/187 (56.7)	BRO 3 mg – AFL 2 mg -11.3 (-20.6, -1.7) BRO 6 mg – AFL 2 mg -5.8 (-14.6, 3.7)
≥15 letters gain from baseline or BCVA ≥84 letters at Week 52	65/190 (34.2)	70/189 (37.0)	73/187 (39.0)	BRO 3 mg – AFL 2 mg -6.2 (-16.0, 3.6) BRO 6 mg – AFL 2 mg -4.1 (-13.3, 5.9)

- BRO 3 mg = Brolucizumab 3 mg; BRO 6 mg = Brolucizumab 6 mg; AFL 2 mg = Aflibercept 2 mg
- n = number of subjects satisfying the criteria of the response variable.
- M = number of subjects with an assessment of the criterion.

[1] Estimate of treatment difference from statistical model using logistic regression adjusting for baseline BCVA

B2302 Study

Table 19: Gain in BCVA (letters read): number (%) of subjects who gained >= 5, 10, or 15 letters in BCVA from baseline or reached BCVA >= 84 letters for the study eye at Week 52 (FAS – LOCF)

Secondary Endpoint	Brolucizumab 6 mg N=179 n/M (%)	Aflibercept 2 mg N=181 n/M (%)	Comparison brolucizumab vs. aflibercept (%) [1]	95% CI for Difference [2]
Proportion of subjects with ≥5 letters gain from baseline or reached BCVA of ≥84 letters at Week 52	139/179 (77.7)	143/181 (79.0)	0.4	(-7.6, 8.9)
Proportion of subjects with ≥10 letters gain from baseline or reached BCVA of ≥84 letters at Week 52	110/179 (61.5)	106/181 (58.6)	5.4	(-3.9, 14.7)
Proportion of subjects with ≥15 letters gain from baseline or reached BCVA of ≥84 letters at Week 52	83/179 (46.4)	68/181 (37.6)	9.6	(-0.4, 20.2)

n = number of subjects satisfying the criteria of the response variable.
M = number of subjects with an assessment of the criterion.
[1] Estimate of treatment difference from statistical model using logistic regression adjusting for baseline BCVA categories (<=65, >65 letters), age categories (<65, >=65 years) and treatment as fixed effect factors.
[2] 95% CI for the treatment difference estimated using bootstrap method.
BCVA assessments after start of alternative DME treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment.
Source: Table 14.2-3.6, Table 14.2-3.7, Table 14.2-3.8

- ***Proportion of subjects with BCVA loss of >=5, >=10 and >=15 ETDRS letters from baseline***

B2301 Study

Table 20: Loss in BCVA (letters read): number (%) of subjects who lost >=15 letters in BCVA from baseline at Week 52 for the study eye (FAS – LOCF)

CHMP assessment report
EMA/23630/2020 Page 56/125

	Brolucizumab 3 mg N=190	Brolucizumab 6 mg N=189	Aflibercept 2 mg N=187
≥15-letter loss from baseline at Week 52			
Proportion of subjects - n/M (%)	3/190 (1.6)	0/189	1/187 (0.5)
95% CI [1]	(0.3, 4.5)	(0.0, 1.9)	(0.0, 2.9)
Comparison of Brolucizumab 3 mg vs. Aflibercept 2 mg [2]			
Proportion estimates (%)	1.6		0.5
Difference - %	1.1		
95% CI for treatment difference	(-1.0, 3.3)		
Comparison of Brolucizumab 6 mg vs. Aflibercept 2 mg [2]			
Proportion estimates (%)		0.0	0.7
Difference - %		-0.7	
95% CI for treatment difference		(-2.7, -0.6)	

n = number of subjects satisfying the criteria of the response variable. M = number of subjects with an assessment of the criterion.
[1] 95% CI for binomial proportions is based on Clopper-Pearson exact method.
[2] Statistical model used logistic regression adjusting for baseline BCVA categories (≤65, >65 letters), age categories (<65, ≥65 years) and treatment as fixed effect factors.
95% CI for the treatment difference estimated using bootstrap method.
BCVA assessments after start of alternative DME treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment.
Source: Table 14.2-3.17

B2302 Study

Table 21: Loss in BCVA (letters read): number (%) of subjects who lost >= 5, 10, and 15 letters in BCVA from baseline at Week 52 for the study eye (FAS – LOCF)

Secondary Endpoint	Brolucizumab 6 mg N=179 n/M (%)	Aflibercept 2 mg N=181 n/M (%)	Comparison brolucizumab vs. aflibercept (%) [1]	95% CI for Difference [2]
Proportion of subjects with ≥5 letters loss from baseline at Week 52	6/179 (3.4)	6/181 (3.3)	-0.4	(-4.2, 2.9)
Proportion of subjects with ≥10 letters loss from baseline at Week 52	4/179 (2.2)	4/181 (2.2)	-0.2	(-3.2, 2.4)
Proportion of subjects with ≥15 letters loss from baseline at Week 52	2/179 (1.1)	3/181 (1.7)	-0.7	(-3.2, 1.6)

n = number of subjects satisfying the criteria of the response variable.
M = number of subjects with an assessment of the criterion.
[1] Estimate of treatment difference from statistical model using logistic regression adjusting for baseline BCVA categories (<=65, >65 letters), age categories (<65, >=65 years) and treatment as fixed effect factors.
[2] 95% CI for the treatment difference estimated using bootstrap method.
BCVA assessments after start of alternative DME treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment.
Source: Table 14.2-3.15, Table 14.2-3.16, Table 14.2-3.17

- ***VFQ-25 at Week 28 and Week 52***

B2301 Study

At Week 28, the improvement in the VFQ-25 overall score (composite score) was comparable across treatment arms, as assessed by the change from baseline in the score. At Week 28, the LS mean differences were -1.9 (95% CI: [-4.2, 0.3]) for brolucizumab 6 mg and -0.9 (95% CI: [-3.0, 1.2]) for brolucizumab 3 mg.

At Week 52, similar improvements in the VFQ-25 overall score were observed, with comparable improvements across treatment arms (LS mean differences of -1.0, 95% CI: [-3.4, 1.4] for brolucizumab 6 mg and -2.3, 95% CI: [-4.7, 0.1] for brolucizumab 3 mg) and no noticeable differences observed across subscales.

Table 22: VFQ-25 overall scores: ANCOVA for change from baseline by visit (FAS – Observed)

CHMP assessment report
EMA/23630/2020 Page 57/125

Composite score Visit	Brolucizumab 3 mg N=190	Brolucizumab 6 mg N=189	Aflibercept 2 mg N=187
Week 28			
n	165	173	168
LS mean estimate (Brolucizumab 3 mg vs. Aflibercept 2 mg)	6.2		7.1
LS mean estimate (Brolucizumab 6 mg vs. Aflibercept 2 mg)		5.9	7.9
LS mean difference (95% CI) (Brolucizumab - Aflibercept)	-0.9 (-3.0, 1.2)	-1.9 (-4.2, 0.3)	
Week 52			
n	151	148	157
LS mean estimate (Brolucizumab 3 mg vs. Aflibercept 2 mg)	5.4		7.7
LS mean estimate (Brolucizumab 6 mg vs. Aflibercept 2 mg)		7.1	8.1
LS mean difference (95% CI) (Brolucizumab - Aflibercept)	-2.3 (-4.7, 0.1)	-1.0 (-3.4, 1.4)	

n = number of subjects with a non-missing value at baseline and the corresponding post-baseline visit.
Analyzed using ANCOVA model with treatment as a fixed effect factor and corresponding baseline value of the endpoint as a covariate.
Data after start of alternative DME treatment in the study eye are censored and are not included in this analysis.
Source: Table 14.2-8.14

B2302 Study

At Week 28, there was no difference between the treatment arms in terms of improvement of the VFQ-25 overall score (composite score) and of each subscale, as assessed by the change from baseline in the score (see SAP in Appendix 16.1.9-Section 2.11). At Week 52, an improvement (LS mean change from baseline) was observed in the brolucizumab arm compared to the aflibercept arm for the VFQ-25 overall score (LS mean difference of 2.5; 95% CI: [0.2, 4.8]) and was mainly driven by the following subscales: role difficulties (4.2, 95% CI: [-0.5, 9.0]), dependency (4.0; 95% CI: [0.1, 7.9]), mental health (3.6, 95% CI: [-0.8, 8.0]), distance activities (3.5; 95% CI: [0.3, 6.7]), and social functioning (3.0; 95% CI: [0.4, 5.5]).

Table 23: VFQ-25 overall score: ANCOVA for change from baseline by visit (FAS – Observed)

Composite Score Visit		Brolucizumab 6 mg N=179	Aflibercept 2 mg N=181
Week 28	n	166	168
	LS mean estimate	5.9	6.1
	LS mean difference (95% CI) (Brolucizumab-Aflibercept)	-0.2 (-2.3, 1.9)	
Week 52	n	143	150
	LS mean estimate	9.1	6.5
	LS mean difference (95% CI) (Brolucizumab-Aflibercept)	2.5 (0.2, 4.8)	

Subgroup analysis

- ***Change from baseline in BCVA at Week 52***

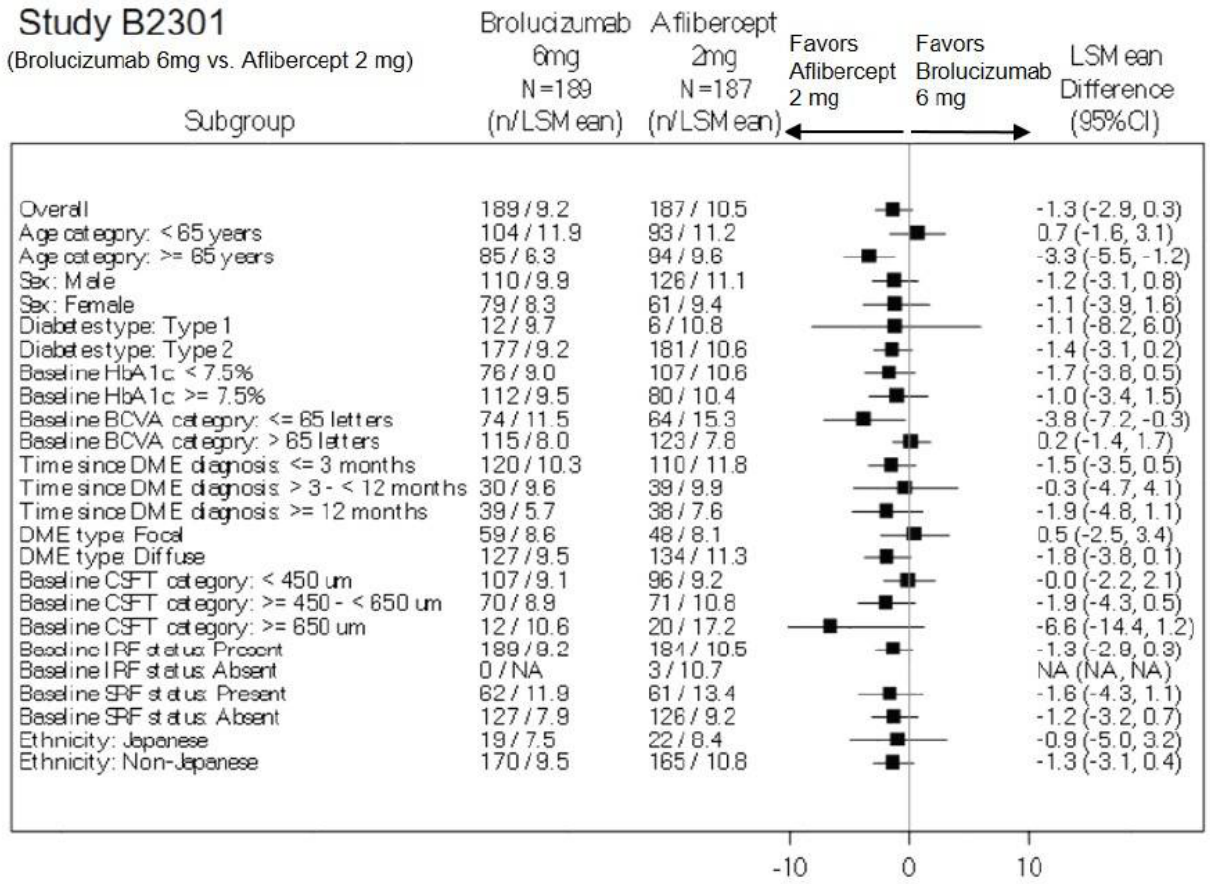
B2301 Study

The LS mean differences between the brolucizumab 6 mg arm and the aflibercept 2 mg arm by subgroup were generally consistent with the one estimated for the overall population, and showed a small numerical treatment difference in favor of aflibercept.

CHMP assessment report
EMA/23630/2020 Page 58/125

The subgroup of subjects without IRF at baseline could not be analyzed because of the very low number of subjects qualifying (i.e., all subjects in the brolucizumab arms had IRF at baseline and only 3 subjects in the aflibercept 2 mg arm had no IRF at baseline).

Figure 5: B3201 BCVA (letters read): Forest plot of ANOVA results for change from baseline at Week 52 for the study eye by subgroup of interest (FAS – LOCF)



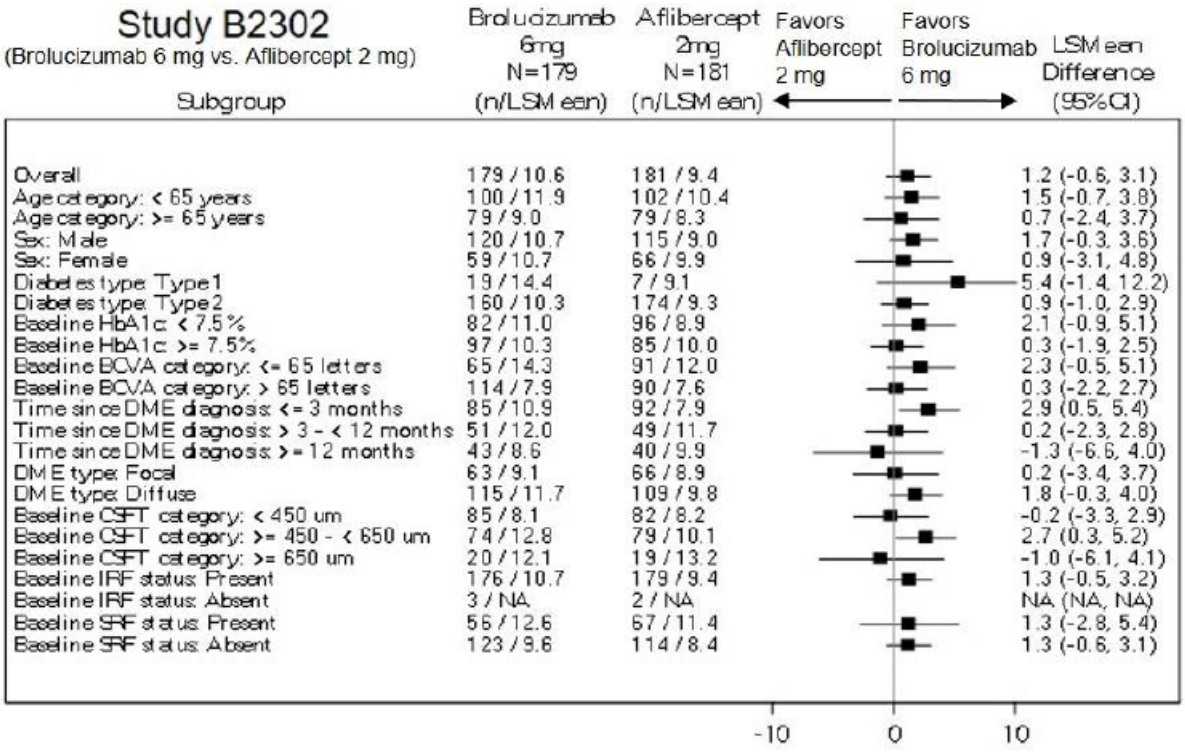
LS Mean estimate difference for brolucizumab – aflibercept (positive value for estimate favors brolucizumab).
n is the number of subjects with data used in the model.
Analyzed using ANOVA which contains baseline BCVA categories (≤65, >65 letters), age categories (<65, ≥65 years) and treatment as fixed effect factors.
For subgroup analyses by baseline BCVA and age categories, the corresponding fixed effect factors are removed from the model.
BCVA assessments after start of alternative DME treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment.
Source: Table 14.2-1.1, Table 14.2-1.7

B2302 Study

The results of the subgroup analyses up to Week 52 showed a relevant benefit in terms of BCVA improvement from baseline for all subgroups (subgroup of subjects without IRF at baseline could not be analyzed because of the very low number of subjects qualifying).

Figure 6: BCVA (letters read): Forest plot of ANOVA results for change from baseline at Week 52 for the study eye by subgroup of interest (FAS – LOCF)

CHMP assessment report
EMA/23630/2020 Page 59/125



LS Mean estimate difference for Brolucizumab – Aflibercept (positive value for estimate favors brolucizumab).
n is the number of subjects with data used in the model.
Analyzed using ANOVA which contains baseline BCVA categories (<=65, >65 letters), age categories (<65, >=65 years) and treatment as fixed effect factors.
For subgroup analyses by baseline BCVA and age categories, the corresponding fixed effect factors are removed from the model.
BCVA assessments after start of alternative DME treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment.
Source: Table 14.2-1.1, Table 14.2-1.7

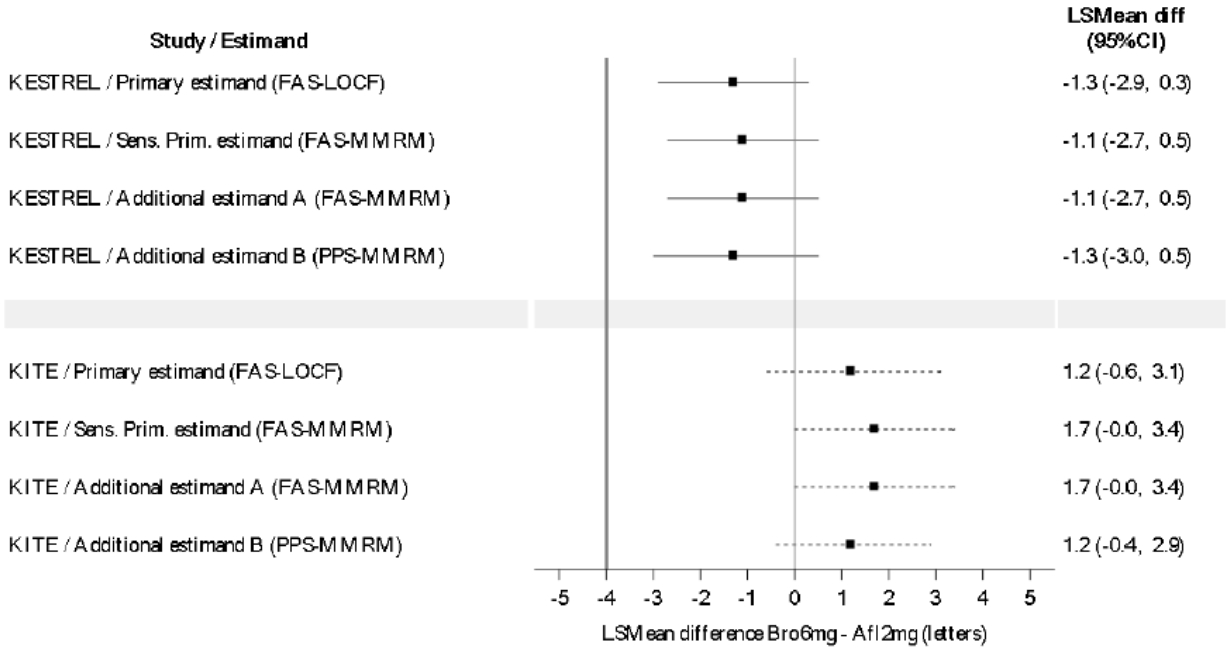
- ***Analyses addressing different Estimands***

As expressed above, additional Estimands (Estimand A with all events handled with treatment policy and Estimand B with all events treated with hypothetical strategy) were requested to aid the interpretation of the main results.

The results are shown below and do not raise any concern.

CHMP assessment report
EMA/23630/2020 Page 60/125

Figure 15-1 Supplementary analyses for additional estimands for the primary endpoint, change from baseline in BCVA at Week 52, in KESTREL and KITE



- ***Timing and occurrence of intercurrent events***

Further to a question by the CHMP, the Applicant has submitted information on the occurrence and timing of the main intercurrent events. The data are reported below and do not raise any further concerns.

Table EMA D90LoQ_Q15-5_KESTREL
Frequency and timing of intercurrent events (ICEs)
Full Analysis Set

	Brolucizumab 3mg N=190	Brolucizumab 6mg N=189	Aflibercept 2mg N=187
Treatment discontinuation due to any reason			
Yes	23 (12.1)	25 (13.2)	18 (9.6)
No	167 (87.9)	164 (86.8)	169 (90.4)
Time to the ICE (weeks)			
n	23	25	18
Mean	24.25	35.90	30.14
SD	15.380	13.429	17.856
Min	3.1	4.1	0.1
Q1	13.14	30.86	16.29
Median	19.29	40.14	32.64
Q3	42.00	44.71	45.00
Max	53.0	51.9	54.1

CHMP assessment report
EMA/23630/2020 Page 61/125

Table EMA D90LoQ_Q15-5_KESTREL
Frequency and timing of intercurrent events (ICEs)
Full Analysis Set

	Brolucizumab 3mg N=190	Brolucizumab 6mg N=189	Aflibercept 2mg N=187
Start of alternative DME treatment			
Yes	2 (1.1)	1 (0.5)	1 (0.5)
No	188 (98.9)	188 (99.5)	186 (99.5)
Time to the ICE (weeks)			
n	2	1	1
Mean	32.14	8.43	8.00
SD	5.859	NA	NA
Min	28.0	8.4	8.0
Q1	28.00	8.43	8.00
Median	32.14	8.43	8.00
Q3	36.29	8.43	8.00
Max	36.3	8.4	8.0

Table EMA D90LoQ_Q15-5_KITE
Frequency and timing of intercurrent events (ICEs)
Full Analysis Set

	Brolucizumab 6mg N=179	Aflibercept 2mg N=181
Treatment discontinuation due to any reason		
Yes	19 (10.6)	15 (8.3)
No	160 (89.4)	166 (91.7)
Time to the ICE (weeks)		
n	19	15
Mean	31.17	28.66
SD	15.167	14.719
Min	4.3	8.1
Q1	19.00	12.43
Median	32.29	28.57
Q3	45.57	41.00
Max	52.3	54.3

CHMP assessment report
EMA/23630/2020 Page 62/125

Table EMA D90LoQ_Q15-5_KITE
Frequency and timing of intercurrent events (ICEs)
Full Analysis Set

	Brolucizumab 6mg N=179	Aflibercept 2mg N=181
Start of alternative DME treatment		
Yes	1 (0.6)	0
No	178 (99.4)	181 (100)
Time to the ICE (weeks)		
n	1	0
Mean	39.14	NA
SD	NA	NA
Min	39.1	NA
Q1	39.14	NA
Median	39.14	NA
Q3	39.14	NA
Max	39.1	NA

- ***Tipping point analysis for the primary estimand***

The primary estimator for the primary estimand assumed MAR. However, MNAR is equally credible in this clinical context. Accordingly, the CHMP has asked the applicant to assess the sensitivity of the results on the primary analysis to violations of the MAR assumption.

Results of the tipping point analyses for the primary estimand in KESTREL and KITE (Table 16-1) are shown below. In KESTREL, the size of the negative shift needed to revert the conclusion of non-inferiority was found to be -7 letters, i.e., approximately 7 times that of the treatment difference between brolucizumab 6 mg and aflibercept 2 mg, whereas in KITE, the size of the tipping point was -19 letters, i.e., approximately 19 times that of the treatment difference between brolucizumab 6 mg and aflibercept 2 mg. In both studies, the tipping point is larger than the NIM of -4 letters. Therefore, results of this sensitivity analysis support the conclusions of the primary analysis.

CHMP assessment report
EMA/23630/2020 Page 63/125

Table 16-1 **BCVA (letters read): Tipping point analysis results for the primary estimand for change from baseline at Week 52 for the study eye in KESTREL and KITE (FAS)**

Study	Brolucizumab 6 mg vs Aflibercept 2 mg	
Delta adjustment (letters)	LS Mean (SE)	(95% CI)
KESTREL		
0	-1.2 (0.82)	(-2.8, 0.4)
4	-1.9 (0.84)	(-3.6, -0.3)
5	-2.1 (0.84)	(-3.8, -0.5)
6	-2.3 (0.85)	(-4.0, -0.6)
7	-2.5 (0.86)	(-4.2, -0.8)
8	-2.7 (0.87)	(-4.4, -1.0)
KITE		
0	1.7 (0.93)	(-0.1, 3.5)
16	-1.3 (1.09)	(-3.4, 0.8)
17	-1.5 (1.11)	(-3.7, 0.7)
18	-1.7 (1.13)	(-3.9, 0.5)
19	-1.9 (1.14)	(-4.1, 0.4)
20	-2.1 (1.16)	(-4.3, 0.2)

- Missing data are imputed using a regression based multiple imputation (MI) method.
- A delta of 0 represents a standard analysis with MI assuming missing at random for all treatment groups.
- Analyzed using an ANOVA model with baseline BCVA categories (<=65, >65 letters), age categories (<65, >=65 years) and treatment as fixed effect factors.
- BCVA assessments after start of alternative DME treatment in the study eye are censored.
- Non-inferiority margin = 4 letters.

Source: Table Q16-1_KESTREL, Table Q16-1_KITE

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 24: Summary of Efficacy for trial B2301 (KESTREL study)

Title: A two-year, three-arm, randomized, double masked, multicenter, phase III study assessing the efficacy and safety of brolucizumab versus aflibercept in adult patients with visual impairment due to diabetic macular edema (KESTREL)		
Study identifier	CRTH258B2301	
Design	Randomized, double-masked, multicenter, active-controlled clinical trials to compare the efficacy and safety of brolucizumab 3 mg and brolucizumab 6 mg versus aflibercept 2 mg (Eylea®), in subjects with visual impairments due to Diabetic Macular Edema (DME) versus aflibercept 2 mg IVT (Eylea®).	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	100 weeks not applicable not applicable
Hypothesis	Non-inferiority	

CHMP assessment report
EMA/23630/2020 Page 64/125

Treatments groups	Experimental : low dose		Brolucizumab 3 mg. 96 weeks, n=190
	Experimental : high dose		Brolucizumab 6 mg. 96 weeks, n=189
	Active comparator		Aflibercept 2 mg. 96 weeks, n=187
Endpoints and definitions	Primary endpoint	Change from baseline in BCVA at Week 52	Letters (EDTRS)
	First key secondary endpoint	Average change in BCVA from Baseline over the period Week 40 through Week 52	Letters (EDTRS)
Database lock	11-Nov-2020		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	other: FAS Week 52			
Descriptive statistics and estimate variability	Treatment group	Brolucizumab 3 mg	Brolucizumab 6 mg	Aflibercept 2 mg
	Number of subject	190	189	187
	Primary endpoint	7.3 (SE: 0.66)	9.2 (SE: 0.57)	10.5 (SE: 0.57)
	Change from baseline in BCVA at Week 52	(95% CI: 6.0, 8.6)	(95% CI: 8.1, 10.3)	(95% CI: 9.4, 11.7)
	First key secondary endpoint	7.0 (SE: 0.63)	9.0 (SE: 0.53)	10.5 (SE: 0.53)
	Average change in BCVA from Baseline over the period Week 40 through Week 52	(95% CI: 5.8, 8.3)	(95% CI: 7.9, 10.0)	(95% CI: 9.4, 11.5)

Effect estimate per comparison	Primary endpoint	Comparison groups	Brolucizumab 3 mg vs Aflibercept 2 mg
		Difference (SE)	-3.3 (0.94)
		95% CI	(-5.1, -1.4)
		P-value	0.227
	Primary endpoint	Comparison groups	Brolucizumab 6 mg vs Aflibercept 2 mg
		Difference (SE)	-1.3 (0.81)
		95% CI	(-2.9, 0.3)
		P-value	<0.001
	First key secondary endpoint	Comparison groups	Brolucizumab 3 mg vs Aflibercept 2 mg
		Difference (SE)	-3.5 (0.90)
		95% CI	(-5.2, -1.7)
		P-value	/
	First key secondary endpoint	Comparison groups	Brolucizumab 6 mg vs Aflibercept 2 mg
		Difference (SE)	-1.5 (0.75)
		95% CI	(-3.0, -0.0)

CHMP assessment report
EMA/23630/2020 Page 65/125

		P-value	<0.001
Notes	Non-inferiority in mean change from baseline in BCVA at Week 58 was met in Per Protocol analysis for brolucizumab 6 mg		

Table 25: Summary of Efficacy for trial B2302 (KITE study)

Title: A two-year, two-arm, randomized, double masked, multicenter, phase III study assessing the efficacy and safety of brolucizumab versus aflibercept in adult patients with visual impairment due to diabetic macular edema (KITE)				
Study identifier	CRTH258B2302			
Design	Randomized, double-masked, multicenter, active-controlled clinical trials to compare the efficacy and safety of brolucizumab 6 mg versus aflibercept 2 mg (Eylea®), in subjects with visual impairments due to Diabetic Macular Edema (DME) versus aflibercept 2 mg IVT (Eylea®).			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	100 weeks not applicable not applicable		
Hypothesis	Non-inferiority			
Treatments groups	Experimental : high dose	Brolucizumab 6 mg. 96 weeks, n=179		
	Active comparator	Aflibercept 2 mg. 96 weeks, n=181		
Endpoints and definitions	Primary endpoint	Change from baseline in BCVA at Week 52		
	First key secondary endpoint	Average change in BCVA from Baseline over the period Week 40 through Week 52		
Database lock	29-Jun-2020			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	other: FAS Week 52			
Descriptive statistics and estimate variability	Treatment group	Brolucizumab 6 mg	Aflibercept 2 mg	/
	Number of subject	190	189	/
	Primary endpoint	10.6 (SE: 0.66)	9.4 (SE: 0.66)	/
	Change from baseline in BCVA at Week 52	(95% CI: 9.3, 11.9)	(95% CI: 8.1, 10.7)	/
	First key secondary endpoint	10.3 (SE: 0.62)	9.4 (SE: 0.62)	/
	Average change in BCVA from Baseline over the period Week 40 through Week 52	(95% CI: 9.1, 11.5)	(95% CI: 8.2, 10.6)	/
Effect estimate per comparison	Primary endpoint	Comparison groups	Brolucizumab 6 mg vs Aflibercept 2 mg	

CHMP assessment report
EMA/23630/2020 Page 66/125

		Difference (SE)	1.2 (0.94)
		95% CI	(-0.6, 3.1)
		P-value	<0.001
	First key secondary endpoint	Comparison groups	Brolucizumab 6 mg vs Aflibercept 2 mg
		Difference (SE)	0.9 (0.88)
		95% CI	(-0.9, 2.6)
		P-value	<0.001
Notes	Non-inferiority in mean change from baseline in BCVA at Week 58 was met in Per Protocol analysis for brolucizumab 6 mg		

Analysis performed across trials (pooled analyses and meta-analysis)

For the purpose of assessing the potential benefit of treatment with brolucizumab 6 mg in a larger group of subjects with DME on the underlying DR, pooled data (E-db) from Study B2301 and Study B2302 for the secondary endpoint related to ≥2-step improvement from baseline in DRSS at Week 52 was analyzed.

Given that the primary objective in each Phase III study was met (see section on Statistical methods), the statistical test of the non-inferiority of the pooled DRSS data was performed.

The Baseline DRSS characteristics at baseline are presented below.

Table 26: Baseline diabetic retinopathy severity in the study eye (E-db, Full Analysis Set)

	Brolucizumab 6mg N = 368 m (%)	Aflibercept 2mg N = 368 m (%)	Overall N = 736 m (%)
Diabetic Retinopathy Severity Scale			
n	362	361	723
1- DR absent	3 (0.8)	1 (0.3)	4 (0.6)
2- Microaneurysms only	1 (0.3)	5 (1.4)	6 (0.8)
3- Mild NPDR	106 (29.3)	89 (24.7)	195 (27.0)
4- Moderate NPDR	109 (30.1)	127 (35.2)	236 (32.6)
5- Moderately severe NPDR	45 (12.4)	36 (10.0)	81 (11.2)
6- Severe NPDR	71 (19.6)	74 (20.5)	145 (20.1)
7- Mild PDR	12 (3.3)	14 (3.9)	26 (3.6)
8- Moderate PDR	11 (3.0)	10 (2.8)	21 (2.9)
9- High-risk PDR	4 (1.1)	4 (1.1)	8 (1.1)
10- Very high-risk PDR	0	0	0
11- Advanced PDR	0	1 (0.3)	1 (0.1)
12- Very advanced PDR	0	0	0
Diabetic Retinopathy Severity Subgroup			
n	362	361	723
Moderate NPDR or better	219 (60.5)	222 (61.5)	441 (61.0)
Moderately severe NPDR or worse	143 (39.5)	139 (38.5)	282 (39.0)

- n = number of subjects with an assessment.
- m = number of subjects with assessment meeting the criterion for the given categorical variables.
- Percentages (%) are calculated based on n.
- DR = Diabetic Retinopathy, NPDR = Non-proliferative Diabetic Retinopathy, PDR =Proliferative Diabetic Retinopathy.

Source: [SCE Appendix 1-Table a1-1]

Non-inferiority of brolucizumab 6 mg compared to aflibercept 2 mg with respect to the proportion of subjects with ≥2 step improvement in DRSS at Week 52 was achieved, with proportion estimates of 28.9% in the brolucizumab 6 mg arm and 24.9% in the aflibercept 2 mg arm, with a difference of 4.0% (95% CI: -0.6, 8.6; p<0.001), with the lower bound of the 95% CI, -0.6%, above the specified non-inferiority margin of -10% (difference in proportions).

CHMP assessment report
EMA/23630/2020 Page 67/125

The Applicant indicates that similar results were observed with an analysis using the Cochran-Mantel-Haenszel (CMH) method and excluding data after PRP.

Table 27: Diabetic Retinopathy Severity Scale (DRSS): Comparison for proportion of subjects with at least a 2-step improvement from baseline in DRSS at Week 52 for the study eye (E-db, Full Analysis Set – LOCF)

	Brolucizumab 6mg N=368	Aflibercept 2mg N=368
Proportion of subjects - n/M (%)	106/362 (29.3)	89/361 (24.7)
95% CI [1]	(24.6, 34.3)	(20.3, 29.4)
Proportion estimates (%) [2]	28.9	24.9
Comparison of Brolucizumab vs Aflibercept [2]		
Difference - %	4.0	
95% CI for treatment difference	(-0.6, 8.6)	
p-value for non-inferiority (10% margin) (1-sided)	< 0.001	

- n = number of subjects satisfying the criteria of the response variable.
- M = number of subjects with an assessment of the criterion.
- [1] 95% CI for binomial proportions is based on Clopper-Pearson exact method.
- [2] Statistical model used logistic regression adjusting for baseline DRSS (12-level scale <=4, >=5), age category (<65, >=65 years), study (B2301, B2302) and treatment as fixed effect factors. P-value and 95% CI for the treatment difference estimated using bootstrap method.
- DRSS assessments after start of alternative DME treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment.

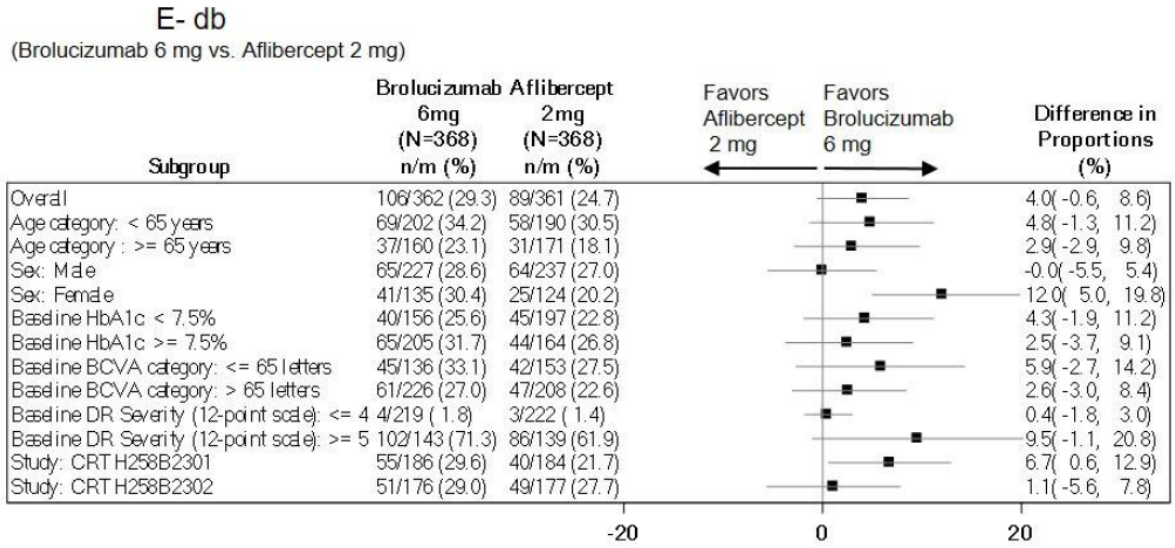
Source: [SCE Appendix 1-Table a2-1.1]

The Applicant explored also data with ≥3 step improvement. The proportion of subjects with a ≥3-step improvement from baseline in the ETDRS DRSS score at Week 52 was comparable between the two treatment arms, with proportion estimates of 17.7% in the brolucizumab 6 mg arm and 16.0% in the aflibercept 2 mg arm with a difference of 1.7% (95% CI: -2.9, 6.3).

Results are also provided for subpopulations.

Table 28: Diabetic Retinopathy Severity Scale (DRSS): Forest plot for difference in proportions of subjects with at least a 2-step improvement from baseline in DRSS at Week 52 for the study eye by subgroup of interest (E-db, Full Analysis Set – LOCF)

CHMP assessment report
EMA/23630/2020 Page 68/125



- n = number of subjects satisfying the criteria of the response variable.
- m = number of subjects with an assessment of the criterion.
- Statistical model used logistic regression adjusting for baseline DRSS (12-level scale <=4, >=5), age category (<65, >=65 years), study (B2301, B2302) and treatment as fixed effect factors. 95% CI for the treatment difference estimated using bootstrap method. Subgroup variables that are used as fixed effects in the model will be removed from the model statement for that subgroup analysis.
- DRSS assessments after start of alternative DME treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment.

Source: [SCE Appendix 1-Table a2-1.1], [SCE Appendix 1-Table a3-1.1]

Additionally, results were consistent with results in each studies.

Table 29: Study B2301 and Study B2302: Comparison for proportion of subjects with at least a 2-step improvement from baseline in DRSS for the study eye

	Study B2301			Study B2302	
	Brolucizumab 3mg N=190	Brolucizumab 6mg N=189	Aflibercept 2mg N=187	Brolucizumab 6mg N=179	Aflibercept 2mg N=181
At Week 28					
Proportion of patients - n/M (%)	44/185 (23.8)	49/186 (26.3)	39/184 (21.2)	44/176 (25.0)	37/177 (20.9)
95% CI [1]	(17.8, 30.6)	(20.2, 33.3)	(15.5, 27.8)	(18.8, 32.1)	(15.2, 27.6)
Comparison of Brolucizumab vs Aflibercept [2]					
Proportion estimates (%)	23.3	25.8	21.7* / 21.7#	24.9	21.0
Difference - %	1.6	4.1		3.9	
95% CI for treatment difference	(-5.3, 8.4)	(-2.1, 10.3)		(-2.5, 10.9)	
At Week 52					
Proportion of patients - n/M (%)	53/185 (28.6)	55/186 (29.6)	40/184 (21.7)	51/176 (29.0)	49/177 (27.7)
95% CI [1]	(22.3, 35.7)	(23.1, 36.7)	(16.0, 28.4)	(22.4, 36.3)	(21.2, 34.9)
Comparison of Brolucizumab vs Aflibercept [2]					
Proportion estimates (%)	28.0	29.0	22.2* / 22.3#	28.9	27.8
Difference - %	5.8	6.7		1.1	
95% CI for treatment difference	(-1.2, 12.4)	(0.6, 12.9)		(-5.6, 7.8)	

n = number of subjects satisfying the criteria of the response variable. M = number of subjects with an assessment of the criterion.
[1] 95% CI for binomial proportions is based on Clopper-Pearson exact method.
[2] Statistical model used logistic regression adjusting for baseline DRSS score categories (≤4, ≥5), age categories (<65, ≥65 years) and treatment as fixed effect factors. 95% CI for the treatment difference estimated using bootstrap method.
* Estimate from the model comparing brolucizumab 6 mg versus aflibercept 2 mg. # Estimate from the model comparing brolucizumab 3 mg versus aflibercept 2 mg.
DRSS assessments after start of alternative DME treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment.
Source: [Study B2301 Wk52-Table 11-14] and [Study B2302 Wk52-Table 11-14]

As intensive blood glucose control reduces the risk of developing retinopathy and reduces the risk of worsening existing diabetic retinopathy, the Applicant was asked to further discuss the adequacy of the control of the diabetes in patients enrolled in the studies, and its potential impact on the results.

CHMP assessment report
EMA/23630/2020 Page 69/125

The Applicant pointed out that an eligible subject was required to have been taking stable diabetic medication(s) within 3 months prior to baseline (inclusion # 4). In addition, the subject's HbA1c at screening should have been < 10% (inclusion #3).

Furthermore, the Applicant showed that an adequate glycemic control at time of subject enrollment was maintained throughout the course of the study. While this ease the interpretation of the results, on the other hand can be seen as a limitation in the knowledge of the effects of brolucizumab in patients with less controlled diabetes. Consequently, the SmPC will state "There is limited experience with Beovu treatment in diabetic patients with HbA1c greater than 10%".

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

To date, intravitreal injections of anti-VEGF (LUCENTIS ® - ranibizumab and EYLEA® - aflibercept) are commonly used in the management of patients with visual impairment secondary to DME.

The Applicant conducted 2 randomized, double-masked, multicenter, active-controlled clinical trials to compare the efficacy and safety of brolucizumab 6 mg, and brolucizumab 3 mg in B2301, versus aflibercept 2 mg (Eylea®), in subjects with visual impairments due to Diabetic Macular Edema (DME). Both studies are conducted versus aflibercept 2 mg IVT (Eylea®). The total studies duration was 100 weeks. The main difference in study design were that B2301 study included a brolucizumab 3 mg treatment arm in addition to the 6 mg arm, while the 6 mg dose only has been investigated in B2302 study.

The general design of the two Phase 3 pivotal studies is appropriate.

The selection criteria are globally consistent with the target population. Both type 1 and type 2 diabetes mellitus are included in the studies. The cut-off defined for Hba1c level (i.e. 10%) and for central subfield retinal thickness (320 µm) are in line with the CHMPA SA of 2016. However, the upper baseline BCVA limit for inclusion was 78 letters. It is supported that source population should reflect current usual practice. However, the inclusion patients with mild impairment and thus having a less room for improvement may not allow to observe a difference between aflibercept and brolucizumab in this subpopulation if exists and drive the non-inferiority. Additionally, there are uncertainties whether the study population is representative enough of the European population. In response to a question from the CHMP, the list of countries where subjects were enrolled, as well as the number of subjects per country, have been provided by the Applicant, reassuring the generalization of the results to the European population.

Patients in brolucizumab arms (3 mg and 6 mg) received 5 loading doses every 6 weeks (q6w) (Day 0, Week 6, Week 12, Week 18 and Week 24), followed by maintenance regimens every 12 weeks (q12w) or every 8 weeks (q8w) depending on the disease activity status. But patients in aflibercept arms received monthly 5 loading doses (Day 0, Week 4, Week 8, Week 12 and Week 16), followed by maintenance regimen every 8 weeks (q8w), and were not allowed to switch on a q12w regimen.

The 3 mg and 6 mg selected doses correspond to the doses selected investigated in the pivotal studies in nAMD (HAWK and HARRIER). This is understood. But, the q6w regimen for the lauding phase is not fully justified. However, considering that efficacy results show that the plateau in gain in BCVA is reached in an acceptable time compared to aflibercept, and the fact that q6w aim to reduce the treatment burden, no further concerns are raised. After the launching phase, patients of the brolucizumab groups were allowed to follow a q12w regimen or a q8w regiment depending on the disease activity assessment. First, despite disease activity is determined by the masked investigator, no defined criteria have been set;

CHMP assessment report
EMA/23630/2020 Page 70/125

recommendation remain vague. Therefore, the absence of well-defined disease activity criteria. In its answer to a question from the CHMP, the Applicant indicates that no defined exact criteria have been set in order to mimic real-world practice. While this is not a conservative approach, this can be understood. Additionally, as the proportion of subjects in the brolucizumab 6 mg arm was maintained on a q12w regimen, meaning with no disease activity, was relatively similar across the two KITE and KESTREL studies, this suggests no large variation across investigators' assessment. Secondly**,** considering that patients of the aflibercept groups were not allowed to switch on the q12w regimen, no comparison between brolucizumab and aflibercept on the total number of injections and the treatment burden can be done. Thirdly, patients from brolucizumab groups were not permitted to switch back on q12w once being on q8w regimen. Therefore extension/re-extension of the interval between injections is not assessed. Finally, at Week 52 (i.e. the primary timepoint), patients were able to achieve a maximum of 2 cycle of treatments on q12w only. However, the 2 years results of the KITE study have been provided in response to a question from the CHMP. While the proportion of brolucizumab subjects by DAA visit within those subjects with no q8w-need during the initial q12w cycle in KITE decreases over the time, a massive drop is not observed during the second year (95% at Week 48 vs 70% at Week 96). Together with the maintenance of the benefice in BCVA at Week 100, this is in favor of the adequacy of the q12w regimen.

More broadly, personalized regimen (*pro re nata* or Treat-and-Extend) were not investigated, in at least one of the two studies or for the second year. However, such treatment strategies are largely used in common practice to manage anti-VEGF IVT medication, in particular to reduce the number of injections, and thus the risk linked to intravitreal injection and the patient burden. Based on the masked investigator's discretion, a 4-week treatment interval extension could be made to the subject's treatment regimen at the time of Week 72 (i.e. prolonging the treatment interval from q8w to q12w, or q12w to q16w). However, starting more personalized treatment at Week 72, while welcomed, does not allow to further investigate the adequacy of such individualized treatment in brolucizumab given the short period of assessment (e.g. only one cycle of treatment for patient under the q16w regimen). Thus, no strong conclusion can be drawn. The Applicant is still encouraged to further investigate personalised regimen for brolucizumab in DME in additional studies. Aflibercept 2 mg IVT (Eylea®) was an appropriate comparator since it can be considered as part of the standard of care for DME.

Overall, objectives and endpoints are acceptable. Testing the non-inferiority of brolucizumab compared to a current standard of care medication (i.e. Eylea®) was appropriate for primary analysis. Additionally, the mean change in BCVA from baseline is an acceptable primary endpoint with clinical relevance in DME. The primary timepoint (i.e. 52 weeks) is also reasonable.

Secondary endpoints were generally acceptable. However, the Applicant did not provide a comprehensive discussion of the ranking of the key secondary endpoints and the endpoints of the hierarchical strategy, and of the clinical significance of this ranking. Additionally, although endpoints on the suitability of the q12w regimen are flagged as key secondary endpoints, there are not part of the hierarchical strategy given no testing analysis can be done; no comparison to aflibercept is possible, so results are descriptive only.

Long term assessments (i.e. Week 100) are planned. Considering that in real life practice many patients are treated for more than 1 years, 24-month data were requested. The 2 years results were provided by the Applicant is response to a question from the CHMP. These support a maintenance of the benefice over the time.

The non-inferiority margin of 4 is considered too broad and therefore not acceptable. However, this is overruled by the actual findings, as the lower limit of the confidence interval is within the 3 letter non-inferiority margin that has been accepted.

CHMP assessment report
EMA/23630/2020 Page 71/125

In each pivotal study, it is noted that both the primary estimand on the FAS and the supplemental estimand on the PPS include a mix of treatment policy strategies and hypothetical strategies depending on the ICE considered. In order to further assess the robustness of the primary and first key secondary analyses, supplementary analyses based on alternative estimands were requested from the Applicant. Overall, the results from these supplementary analyses showed consistency with the primary and sensitivity analysis of the study reports, confirming the robustness of the main efficacy results.

In all primary and first key secondary endpoint analyses, missing data are either imputed using LOCF or based on MAR assumption (in MMRM analyses). However, data are likely MNAR, and it was of interest to assess the potential impact of MNAR data on the results. Therefore, the Applicant was requested to perform tipping point analyses. Based on these results, the impact of MNAR data on the efficacy results should be limited and is not expected to impact the study conclusions.

The multiple testing procedure for the pooled non-inferiority analysis of the DRSS endpoint based on both studies DR2301 and DR2302 is questionable. Nevertheless, the pre-specified pooled analysis is deemed acceptable but requires a careful interpretation of the results, based on both achieved significance levels and their clinical relevance.

The Applicant was requested to clarify the proportion of imputed values by treatment group and by reason for imputation for the pooled DRSS analysis. A sensitivity analysis was also provided where missing/censored values are counted as failures (non-improvement). The sensitivity analyses with missing/censored values imputed as failures showed lower improvements rates in both treatment arms, with a treatment difference that remained consistent with the CSR results. The conclusions remained the same.

Efficacy data and additional analyses

566 subjects were randomized in a 1:1:1 ratio to the brolucizumab 6 mg (n=189) or 3 mg (n=190) arms, or to the aflibercept 2 mg arm (n=187) in the B2301 study, while 360 subjects were randomized in a 1:1 ratio to brolucizumab 6 mg arm (n=179) or aflibercept 2 mg arm (n=181) in the B2302 study.

Overall, the conduct of the study is thus considered acceptable. Additionally, further discussion on the revision of the inclusion criterion number 5 on central subfield retinal thickness regarding the efficacy results was provided by the Applicant in the response to a question from the CHMP reassuring that no impact is anticipated.

Generally, demographic and patients characteristics were well balanced across arms. However, we can observe a significant imbalance in the proportion of patients with a BCVA superior to 65 letters across groups in the B2302 study. The proportion was numerically higher in the brolucizumab group, 63.7%, than in the aflibercept group, 49.7%. But subgroup analysis are reassuring. Additionally, the overall proportion of patients with type I diabetes remains very limited, 4.9 % in B2301 study and 7.2% B2302 study. In the answer to a question from the CHMP, the Applicant indicated that the proportion of Type I diabetes in KESTREL and KITE studies is consistent with the other anti-VEGF studies in DME population. This can be followed. However, no discussion was provided regarding the representativeness of the Type I population. However, considering that no discrepancies are observed in subgroup analysis, this is not of concern.

The mean BCVA at baseline was 65.9 letters and 64.9 letters respectively in B2301 study and B2302 study, while the mean CSFT was 461.5 µm and 482.7 µm respectively in B2301 study and B2302 study.

The time since diagnosis of DME was well balanced among groups, large majority of the patients having a diagnosis inferior to 3 months. Additionally, despite that selection criteria allowed to include subjects

CHMP assessment report
EMA/23630/2020 Page 72/125

with history of periocular or intraocular corticosteroid treatments or laser (with respectively 6 months and 3 months of wash-out), it is unclear whether or non-naïve-treatments patients were enrolled in the study. In its response to a question from the CHMP, the Applicant indicated that no non-treatment-naïve patients were enrolled in KESTREL and KITE studies; no data are thus available. While the current data are sufficient to conclude on the present application, the Applicant should consider to further investigate the efficacy/safety in this subpopulation in the clinical development, evaluating the switch from another anti-VEGF to brolucizumab.

All patients were included in FAS population, in both studies. Additionally, differences in the proportion of subjects included in the Per Protocol population between brolucizumab arms and aflibercept arms remains limited.

According to the primary analysis, the non-inferiority of brolucizumab 6 mg group over the aflibercept group was demonstrated in B2301 and B2301 studies. Analysis in FAS and PPS were consistent, supported by sensitivity analysis and by the first key secondary endpoint, average change in BCVA from Baseline over the period Week 50 through Week 42, for which non-inferiority was also met.

However, the non-inferiority of brolucizumab 3 mg group over the aflibercept group was not achieved for the primary endpoint. As a consequence, the hierarchical strategy was stopped. Therefore, superiority testing of brolucizumab 6 mg vs. aflibercept 2 mg were not performed for following endpoints: Average change from baseline in BCVA over the period Week 40 through Week 52, Average change from baseline in CSFT over the period Week 40 through Week 52 and Presence of subretinal fluid and intraretinal fluid at Week 52.

In B2301 study, regarding FAS population, the mean change in BCVA from Baseline at Week 52, with 95% CI, for Brolucizumab 6 mg and Aflibercept were respectively 9.2 [8.1, 10.3] and 10.5 [9.4, 11.7] letters. In pairwise ANOVA, the non-inferiority of Brolucizumab 6 mg compared to Aflibercept were demonstrated with a LS mean difference -1.3 letters (95% C.I.: -2.9, 0.3; p<0.001).

In B2302 study, regarding FAS population, the mean change in BCVA from Baseline at Week 52, with 95% CI, Brolucizumab 6 mg and Aflibercept were respectively 10.6 [9.3, 11.9] and 9.4 [8.1, 10.7] letters. In pairwise ANOVA, the non-inferiority of Brolucizumab 6 mg compared to Aflibercept were demonstrated with a LS mean difference 1.2 letters (95% C.I.: -0.6, 3.1; p<0.001).

Regarding the assessment of the regimen, second key secondary endpoint estimated with 95% CI that the probability for a subject to be maintained on the q12w regimen up to the disease activity assessment at Week 52 was 55.1% [46.9, 62.5] in B2301 study and 50.3 % [42.5, 57.7] in B2302 study. However, as discussed above, there is too limited cycle of treatment on q12w regimen to properly assess whether or not q12w is appropriate to manage patients with visual impairment secondary to DME. In the response to a question from the CHMP, the Applicant provided the 2 years data of the KITE study. While the proportion of brolucizumab subjects by DAA visit within those subjects with no q8w-need during the initial q12w cycle in KITE decreases over the time, a massive drop is not observed during the second year (95% at Week 48 vs 70% at Week 96). Together with the maintenance of the benefice in BCVA at Week 100, this is in favor of the adequacy of this regimen.

In B2302 study, superiority testing for the change from baseline in CSFT over the period Week 40 through Week 52 reached statistical significance (LS mean difference of -29.4 µm [95% CI: -48.6, -10.2], p=0.001). However this result could not be replicated in the B2301 study, because superiority testing were not allowed (see comment above). Additionally, the superiority was not met for the average change from baseline in BCVA over the period Week 40 through Week 52 (p=0.164). Therefore, the testing sequence was stopped and Presence of subretinal fluid and intraretinal fluid (central subfield) at Week 52 was not tested for superiority.

CHMP assessment report
EMA/23630/2020 Page 73/125

Overall, outcomes in anatomical parameters, in particular mean change in CSFT from Baseline to Week 52 and presence of SRF and/or IRF at Week 52, were supportive of the non-inferiority of 6 mg compared to aflibercept.

Results in responder analysis for BCVA (i.e.: proportion of patients having a gains of at least 15 letters from Baseline or a BCVA >= 84 letters at Week 52), are consistent with primary outcomes for both B2301 and B2302 studies. However, in B2301, proportion of subjects with BCVA gain of >=5 and >=10 TDRS letters from baseline, and proportion of subjects with BCVA gain of >=5 and >=10 ETDRS letters from baseline were not well compiled in the body report. The Applicant has provided such analysis in the response to a question from the CHMP. No discrepancies with main outcomes were noted.

Overall, subgroup analysis showed consistencies across the subpopulations in both B2301 and B2302 studies. This was reassuring, especially regarding imbalances in the B2302 study in the proportion of patients Type 1 diabetes at baseline and the proportion of patients with a BCVA superior to 65 letter at baseline.

Assessment of the Quality of Life was also supportive of the benefice of brolucizumab 6 mg.

Finally, for the purpose of assessing the potential benefit of treatment with brolucizumab 6 mg in a larger group of subjects with DME on the underlying DR, pooled data (E-db) from Study B2301 and Study B2302 for the secondary endpoint related to ≥2-step improvement from baseline in DRSS at Week 52 was analysed. Overall, DRSS characteristics at baseline was well balance across the brolucizumab 6 mg arm and the aflibercept arm. However, given that patients with active PDR are excluded of the study, the proportion of patients with a PDR was very limited making difficult the generalisation of the results in this subset.

Analysis of the proportion of subjects with ≥2-step improvement in DRSS at Week 52 shown a non-inferiority of brolucizumab 6mg versus aflibercept with an estimated difference of 4.0% (95% CI: -0.6, 8.6; p<0.001). The proportion estimates, with 95% CI, were 28.9% [24.6, 34.3] in the brolucizumab 6 mg arm and 24.9% in the aflibercept 2 mg arm [20.3, 29.4]. Results are supported by sensitivity analysis, subgroup analysis and analysis of the proportion of subjects with ≥3-step improvement in DRSS at Week 52.

However, the worsening of diabetic retinopathy, in particular for non-proliferative diabetic retinopathy, can be slow and progress over years. Therefore, a sustained effect over time has to be shown. In the response to a question from the CHMP, the Applicant has provided 24-Month data for DRSS analysis. Overall, results at Week 100 in proportion of subjects with >=2-step improvement from baseline in the DRSS score are consistent with outcomes at Week 52 in both KESTREL and KITE studies. Additionally, intensive blood glucose control reduces the risk of developing retinopathy and reduces the risk of worsening existing diabetic retinopathy. Following the response to a question from the CHMP, the Applicant additional results showing that the HbA1c level seems stable in the brolucizumab and aflibercept groups over the study duration, reassuring adequate controlled diabetes. The downside is that there is no data in patients with poorly controlled diabetes. In line with this, a statement in the SmPC has been introduced whereby "There is limited experience with Beovu treatment in diabetic patients with HbA1c greater than 10%".

Moreover, based on the statistical method, it is challenging to draw any meaningful conclusions regarding the control of the type I error within or across studies. Despite the proposed method this pooled analysis is ultimately accepted, conclusions should be thus interpreted very cautiously.

CHMP assessment report
EMA/23630/2020 Page 74/125

2.4.3. Conclusions on the clinical efficacy

Overall, the clinical development based on 2 randomized, double-masked, multicenter, active-controlled clinical trials, B2301 and B2302 studies, is considered as acceptable. Furthermore, the general design of both pivotal Phase III studies is appropriate.

The results support the demonstration of the non-inferiority of brolucizumab 6 mg compared to aflibercept.

2.5. Clinical safety

Introduction

Key safety data provided consist of the 52-week data analysis from the 2 pivotal Phase III studies in the target indication of DME detailed below.

Study	Study design, objective, population	Total no. of subjects randomized	Study duration	Treatment, dose regimen, number of subjects treated
Active-controlled studies				
CRTH258B2301 (KESTREL)	Phase III, three-arm, randomized, double-masked, multicenter study assessing the efficacy and safety of brolucizumab versus aflibercept in adult patients with visual impairment due to DME	Total: N= 566 Brolucizumab 3 mg: N= 190 Brolucizumab 6 mg: N=189 Aflibercept: N=187	100 weeks total (This study is ongoing. The data reported in this submission refers to the safety analysis up to Week 52 of double-masked treatment period)	Brolucizumab 3 mg: 5 x q6w loading then q12w/q8w maintenance (N=190) Brolucizumab 6 mg: 5 x q6w loading then q12w/q8w maintenance (N=189) Aflibercept 2 mg: 5 x q4w loading then q8w maintenance (N=187)
CRTH258B2302 (KITE)	Phase III, two-arm, randomized, double-masked, multicenter study assessing the efficacy and safety of brolucizumab versus aflibercept in adult patients with visual impairment due to DME	Total: N=360 Brolucizumab 6 mg: N=179 Aflibercept: N=181	100 weeks total (This study is ongoing. The data reported in this submission refers to the safety analysis up to Week 52 of double-masked treatment period).	Total: (N= 360) Brolucizumab 6 mg: 5 x q6w loading then q12w/q8w maintenance (with option to extend to q16w during second year) (N=179) Aflibercept 2 mg: 5 x q4w loading then q8w maintenance (N=181)

q4w: once every 4 weeks, q6w: once every 6 weeks, q8w: once every 8 weeks, q12w: once every 12 weeks, q16w: once every 16 weeks

For this submission, the cut-off dates for last patient completed Week 52 are 11-Nov-2020 for Study B2301 and 29-Jun-2020 for Study B2302.

Safety data for both pivotal Phase III studies is provided up to 52 weeks in the target indication. However, both studies have a treatment period of 100 weeks; therefore long term safety in the DME indication is continuously monitored and this data will become available at study completion.

CHMP assessment report
EMA/23630/2020 Page 75/125

Since the studies have similar designs, assessments and length, and both studies contain brolucizumab 6 mg and aflibercept 2 mg treatment arms with 1 to 1 randomization ratio, the data can be pooled. The study designs allow the comparison of brolucizumab 6 mg and aflibercept 2 mg treatment in terms of safety; in addition, the safety of treatment with brolucizumab 3 mg can be evaluated in Study B2301.

Three different pooled safety databases (S-db) were used to analyze the safety data from the 2 pivotal studies used for this submission.

-Loading S-db 1; P1

This pool included data up to and including Week 28 from the both studies.

During the first 28 weeks of treatment (Week 28) brolucizumab subjects were scheduled to receive 5xq6w injections and aflibercept subjects were scheduled to receive 5xq4w and the first injection in the maintenance phase (8 weeks after last loading dose). Week 28 is 4 weeks after the subjects have received their last active injection in both the brolucizumab and aflibercept arms.

Since the duration of exposure (28 weeks) is the same for the brolucizumab treatment groups and the aflibercept group in this pool, it was mainly used to evaluate the safety during the first 28 weeks after study treatment initiation.

-Loading S-db 2; P2

This pool is a subset of Loading S-db 1 and was created because the loading phase for brolucizumab (5xq6w, 24 weeks) has a longer duration than the loading phase for aflibercept (5xq4w, 16 weeks).

Taking a conservative approach, in this pool, data up to and including Week 28 is included for the brolucizumab treatment groups and data up to and including Week 20 is included for the aflibercept treatment group. Thus, in this pool, subjects in all treatment groups were scheduled to receive 5 injections; however exposure duration differs between brolucizumab (28 weeks) vs. aflibercept (20 weeks).

This pool was used in combination with Loading S-db 1 to evaluate the safety of brolucizumab at Week 28 and aflibercept at Week 20, since the same number of IVT injections (5 injections) had been administered in the brolucizumab and aflibercept treatment arms up to these time points.

-52 week S-db; P3

This pool includes all primary analysis data from both studies. This pool is to evaluate the safety profile of brolucizumab over 52 weeks following treatment compared to that of aflibercept.

Two other studies are ongoing in DME indication:

- CRTH258B2304 (KINGLET): Two-arm, double masked, one year, randomized, multicentre study assessing the efficacy and safety of brolucizumab versus aflibercept in adult Chinese patients with visual impairment due to DME

- CRTH258B2305 (KINGFISHER): Two-arm, double masked, randomized, 12-Month, multicentre study assessing the efficacy and safety of brolucizumab every 4 weeks versus aflibercept every 4 weeks in +adult patients with visual impairment due to DME

CHMP assessment report
EMA/23630/2020 Page 76/125

Patient exposure

- **Exposure to treatment**

-Loading S-db 1; P1

The duration of treatment (Week 28) was the same for the pooled brolucizumab 6 mg group and pooled aflibercept 2 mg group; as expected most of the pooled brolucizumab 6 mg subjects (91.6%) and most of the subjects in the brolucizumab 3 mg group in Study B2301 (85.8%) had received 5 scheduled injections and most of the pooled aflibercept 2 mg subjects (89.9%) had received 6 scheduled injections.

Table 30: Exposure to treatment in the loading phase Sdb-1 and 2

	CRTH258B2301	Pooled		
	28 weeks	28 weeks	28 weeks	20 weeks
Extent of exposure	Bro 3mg N=190	Bro 6mg N=368	Afl 2mg N=368	Afl 2mg N=368
Number of active injections - n (%)				
n	190	368	368	368
1	4 (2.1)	3 (0.8)	3 (0.8)	3 (0.8)
2	5 (2.6)	5 (1.4)	5 (1.4)	6 (1.6)
3	5 (2.6)	8 (2.2)	5 (1.4)	4 (1.1)
4	13 (6.8)	15 (4.1)	0	11 (3.0)
5	163 (85.8)	337 (91.6)	18 (4.9)	338 (91.8)
6	0	0	331 (89.9)	6 (1.6)
7	0	0	6 (1.6)	0
Number of active injections				
n	190	368	368	368
Mean	4.7	4.8	5.8	4.9
SD	0.82	0.60	0.76	0.60
Min	1	1	1	1
Median	5.0	5.0	6.0	5.0
Max	5	5	7	6

-Loading S-db 2; P2

In this database, which by design was to match the number of injections in each pooled treatment group, the proportion of subjects who had received the scheduled number of injections was similar in the pooled brolucizumab 6 mg group (5 injections, 91.6% at Week 28) and pooled aflibercept 2 mg group (5 injections, 91.8% at Week 20).

-52 week S-db; P3

Up to Week 52, the median number of administered active injections was 7 in the pooled brolucizumab 6 mg arms in both Study B2301 and Study B2302 and brolucizumab 3 mg arm in Study B2301 vs. 9 injections in the pooled aflibercept 2 mg group in both Study B2301 and Study B2302.

The percentage of subjects receiving 8 injections (the second highest frequency) in the brolucizumab groups was 29.9% in the pooled brolucizumab 6 mg group and 30.0% in the brolucizumab 3 mg arm of Study B2301.

This difference between the treatment arms was driven by the different IVT injection schedules during the loading phase for each arm of the studies and the changes in IVT injection schedule based on disease activity assessment during the maintenance phase in the brolucizumab arms.

CHMP assessment report
EMA/23630/2020 Page 77/125

Table 31: Exposure to treatment up to week 52

	CRTH258B2301	Pooled	
Extent of exposure	Bro 3mg N=190	Bro 6mg N=368	Afl 2mg N=368
Number of active injections - n (%)			
n	190	368	368
1	4 (2.1)	3 (0.8)	3 (0.8)
2	4 (2.1)	5 (1.4)	5 (1.4)
3	3 (1.6)	4 (1.1)	3 (0.8)
4	6 (3.2)	8 (2.2)	0
5	6 (3.2)	21 (5.7)	4 (1.1)
6	14 (7.4)	18 (4.9)	12 (3.3)
7	96 (50.5)	199 (54.1)	10 (2.7)
8	57 (30.0)	110 (29.9)	30 (8.2)
9	0	0	294 (79.9)
10	0	0	7 (1.9)
Number of active injections			
n	190	368	368
Mean	6.8	6.9	8.5
SD	1.51	1.26	1.39
Min	1	1	1
Median	7.0	7.0	9.0
Max	8	8	10

studies.

- **Subject disposition**

-Loading S-db 1 and 2

The majority of subjects (> 92%) across treatment groups completed the loading phase of the study, without discontinuing study drug, up until Week 28. The frequency of discontinuation of study prior to or at Week 28 was higher in the 3 mg brolucizumab group in Study B2301 (7.4%), compared to the pooled brolucizumab 6 mg group (3.0%) and pooled aflibercept 2 mg group (3.8%).

Similarly, discontinuation of study treatment prior to or at Week 28 was higher in the 3 mg brolucizumab group in Study B2301 (7.9%) compared to the pooled 6 mg brolucizumab (4.3%) and the pooled aflibercept group (4.3%). The most common reason for discontinuation of study drug in the loading phase until Week 28 (whether the subject remained in the study or not) was 'adverse event' for subjects in the 3 mg brolucizumab group in Study B2301 (2.6%); in the pooled 6 mg brolucizumab (1.6%) and in the aflibercept groups (1.6%), followed by 'subject decision' in the 3 mg brolucizumab group in Study B2301 (2.1%); in the pooled 6 mg brolucizumab (1.1%); and in the pooled aflibercept 2 mg group (1.4%).

-52 week S-db

The majority of subjects (> 87%) in both studies completed the 52 week study treatment without permanently discontinuing study drug, with similar proportions of subjects completing across treatment groups.

The most common reasons for discontinuation of study treatment in the 52 week database (whether remaining in the study or not) were 'subject decision' (3.7% of subjects in the 3 mg brolucizumab group

CHMP assessment report
EMA/23630/2020 Page 78/125

in Study B2301; 4.1% in the pooled 6 mg brolucizumab group; and 2.4% in the pooled aflibercept 2 mg group). A similar proportion of subjects discontinued study treatment due to 'adverse event' in the 52 week database in all 3 treatment groups (3.7% of subjects in the 3 mg brolucizumab group in Study B2301; 3.0% in the pooled 6 mg brolucizumab group; and 3.5% in the pooled aflibercept 2 mg group).

Table 32: Subject disposition in 52-week S-db

		CRTH258B2301	Pooled	
	Disposition Reason	Bro 3mg N=190 n (%)	Bro 6mg N=368 n (%)	Afl 2mg N=368 n (%)
	Treated	190 (100)	368 (100)	368 (100)
Study	Completed Week 52[1]	162 (85.3)	299 (81.3)	314 (85.3)
	Ongoing, did not complete Week 52 [2]	9 (4.7)	34 (9.2)	27 (7.3)
	Discontinued prior to or at Week 52	19 (10.0)	35 (9.5)	27 (7.3)
	Subject decision	8 (4.2)	17 (4.6)	8 (2.2)
	Death	1 (0.5)	8 (2.2)	4 (1.1)
	Adverse event	5 (2.6)	6 (1.6)	8 (2.2)
	Lost to follow-up	3 (1.6)	2 (0.5)	4 (1.1)
	Physician decision	1 (0.5)	1 (0.3)	2 (0.5)
	Progressive disease	0	1 (0.3)	0
	Protocol deviation	1 (0.5)	0	1 (0.3)
Study treatment	Completed Week 52 [3]	167 (87.9)	324 (88.0)	335 (91.0)
	Discontinued prior to or at Week 52	23 (12.1)	44 (12.0)	33 (9.0)
	Subject decision	7 (3.7)	15 (4.1)	9 (2.4)
	Adverse event	7 (3.7)	11 (3.0)	13 (3.5)
	Death	1 (0.5)	6 (1.6)	3 (0.8)
	Lost to follow-up	3 (1.6)	4 (1.1)	4 (1.1)
	Physician decision	3 (1.6)	4 (1.1)	0
	Protocol deviation	2 (1.1)	3 (0.8)	4 (1.1)
	Pregnancy	0	1 (0.3)	0

- [1] Completed Week 52 = subjects have a Week 52 visit.
- [2] Subjects missed the Week 52 visit but remain in the study at the time of the Week 52 cutoff.
- [3] Completed Week 52 = subjects completed the Week 52 visit or missed the Week 52 visit but remained on study treatment at the time of the Week 52 cutoff.

- **Patient demographics and baseline characteristics**

Since the 3 different pooled safety databases which were used to analyze the safety data represent the same patient population with different durations of exposure, demographics are described for the Loading safety database 1 only.

Demographics in the Loading safety database 1 were similar across treatment groups. The race of the subject population was predominantly classified as 'White' and the ethnicity of the subject population was predominantly 'not Hispanic or Latino'. The mean age was 62.4- 64.4 years, median 64.0 years, with subjects' age ranging from 23-87 years in the 3 treatment groups. There were more male subjects (62.5-65.5%) than female subjects (34.5-37.5%) in the study population.

Baseline diabetes characteristics were generally comparable across treatment groups in the Loading safety database 1. While the proportion of patients with HbA1c of less than 7.5% was 43% in the 6 mg group and 55% in the aflibercept 2 mg group, the mean HbA1c levels were similar (≤ 10% was required

CHMP assessment report
EMA/23630/2020 Page 79/125

as per eligibility 1-1criteria for adequate glycemic control). The majority of subjects presented with Type 2 diabetes (>91% in all 3 treatment groups). There were more subjects in the 6 mg brolucizumab group with Type I diabetes (8.4%) compared to the 3 mg brolucizumab (5.3%) and aflibercept (3.5%) groups.

Baseline ocular characteristics for the study eye were comparable across the treatment groups in Loading safety database 1. The majority (> 77% in all 3 treatment groups) were diagnosed with DME within 12 months prior to baseline; for the brolucizumab 3 mg group in Study B2301 there was a large variability of time since diagnosis of DME (0-295 months, mean 12.5 months with SD 30.82 months). The mean baseline BCVA in the study eye was comparable across treatment groups (64.5-66.3 letters read) in Loading safety database 1. A greater proportion of subjects had a BCVA of > 65 letters at baseline in all 3 groups (57.9-62.2%) compared to those subjects with BCVA ≤ 65 letters at baseline. The mean CSFT was similar across treatment groups (456.0-479.9 µm).

More comprehensive data are provided in Efficacy part.

- **Prior and concomitant medications or treatments**

There were a similar proportion of subjects (5.7% of subjects in the 6 mg brolucizumab and 6.3% of the aflibercept group) in the Loading safety database 1, who had prior ocular medications for the study eye. The proportion of subjects who had prior non-ocular medications was comparable (12.0% of subjects in the 6 mg brolucizumab group and 10.6% of the aflibercept group) in the Loading safety database 1.

A similar proportion of subjects (20.9% of subjects in the 6 mg brolucizumab group and 20.4% of the aflibercept group) in the Loading safety database 1, took concomitant ocular medications for the study eye at least once during the treatment period. As expected in this DME subject population, almost all subjects were taking non-ocular medications concomitantly during the treatment period (100% of subjects in the 6 mg brolucizumab group and 99.2% of the aflibercept group in the Loading safety database 1

Medications with a start date after the start date of treatment with an alternative DME treatment are not included.

Adverse events

1- COMMON AE

AE incidences are summarized for all the 3 pooled safety databases. These S-dbs represent the same patient population with different durations of exposure.

Loading safety database 1: the duration of exposure is the same for the brolucizumab treatment arms and the aflibercept arm in this pool, this pool was mainly for evaluating the non-ocular safety during the 28 week loading phase.

Loading safety database 2 is a subset of Loading safety database 1; this pool is used to evaluate the ocular safety between the brolucizumab 28 week (4 weeks following the loading phase) and the aflibercept 20 week (4 weeks following the loading phase) since both pools include the same number of injections. This database was planned to take a conservative approach focusing more on events possibly related to number of injections (5 x loading). The incidence of ocular AEs in the study eye was generally comparable between brolucizumab and aflibercept in the Loading safety database 1&2. Therefore, the results of the Loading safety database 1 are mainly explained in this document, and the results of the Loading safety database 2 are presented in the tables.

CHMP assessment report
EMA/23630/2020 Page 80/125

The 52 week safety database includes all primary analysis data from Study B2301 and Study B2302. This pool is to evaluate the overall safety during the 52 weeks of treatment.

- **Loading s-db 1 and 2**

-Ocular AE

At Week 28 in P1, subjects in the pooled brolucizumab 6 mg group and brolucizumab 3 mg group in Study B2301 were scheduled to receive 5 injections, and subjects in the pooled aflibercept 2 mg group were scheduled to receive 6 injections. The proportion of subjects experiencing at least 1 ocular AE in the study eye was similar between the pooled brolucizumab 6 mg group (24.2%) and pooled aflibercept 2 mg group (25.0%) at Week 28 (Table 33**: Ocular AE in S-db 1 & 2**). In Study B2301 the proportion of subjects in the brolucizumab 3 mg group who had at least 1 ocular AE was 33.2%.

Conjunctival hemorrhage was the most commonly reported ocular AE in the study eye in Loading safety database 1 and occurred in a similar proportion of subjects in the pooled brolucizumab 6 mg group (17 subjects; 4.6%) and pooled aflibercept 2 mg group (21 subjects; 5.7%). Conjunctival hemorrhage was reported in 14 subjects (7.4%) in the brolucizumab 3 mg group of Study B2301.

Table 33: Ocular AE in S-db 1 & 2

	CRTH258B2301	Pooled		
	28 weeks	28 weeks	28 weeks	20 weeks
Preferred Term	Bro 3mg N=190 n (%)	Bro 6mg N=368 n (%)	Afl 2mg N=368 n (%)	Afl 2mg N=368 n (%)
Number of subjects with at least one AE	63 (33.2)	89 (24.2)	92 (25.0)	78 (21.2)
Conjunctival haemorrhage	14 (7.4)	17 (4.6)	21 (5.7)	18 (4.9)
Vitreous floaters	6 (3.2)	11 (3.0)	6 (1.6)	5 (1.4)
Eye pain	4 (2.1)	8 (2.2)	3 (0.8)	3 (0.8)
Dry eye	6 (3.2)	7 (1.9)	6 (1.6)	6 (1.6)
Vitreous detachment	7 (3.7)	6 (1.6)	1 (0.3)	0
Vision blurred	5 (2.6)	1 (0.3)	4 (1.1)	4 (1.1)
Conjunctival hyperaemia	4 (2.1)	0	1 (0.3)	1 (0.3)

At Week 28, the most frequently reported SOC was eye disorders (21.5% of subjects in the pooled brolucizumab 6 mg group and 23.4% of subjects in the pooled aflibercept 2 mg group); in Study B2301 in the brolucizumab 3 mg group it was 32.6%.

Treatment-related AE

In the Loading safety database 1 & 2, at Week 28, 2.2% of subjects in the pooled brolucizumab 6 mg group and 0.8% of subjects in the pooled aflibercept 2 mg group had at least 1 AE suspected by the Investigator to be related to study drug, whereby all AEs were classified in the SOC of Eye disorders in both treatment groups; apart from 1 AE (0.3%) in the SOC of Investigations (PT of IOP increased in the brolucizumab 6 mg group. At Week 28, in the brolucizumab 3 mg group, 3.2% of subjects had at least 1 AE suspected by the Investigator to be related to study drug, whereby all AEs were classified in the SOC of Eye disorders; apart from 1 AE (0.5%) in the SOC of Investigations (PT of IOP increased).

The most frequently reported ocular AEs suspected by the Investigator to be related to the study treatment, at Week 28, were uveitis 2 subjects (0.5%) in pooled the brolucizumab 6 mg group, 1 subject (0.3%) in the pooled aflibercept 2 mg group; and iridocyclitis 2 subjects (0.5%) in the pooled brolucizumab 6 mg group and 0 subjects in the pooled aflibercept 2 mg group.

CHMP assessment report
EMA/23630/2020 Page 81/125

Severity

In Loading safety database 1, at Week 28, the majority of ocular AEs in the study eye were considered to have a maximum severity which was mild or moderate. The proportion of subjects having mild or moderate ocular AEs of the study eye was similar across all treatment groups (22.6 % in the pooled brolucizumab 6 mg group, 23.9% in the pooled aflibercept 2 mg group and 31.6% in brolucizumab 3 mg group in Study B2301. The proportion of subjects with severe ocular AEs was similar across treatment groups (6 subjects; 1.6 % in the pooled brolucizumab 6 mg group, 4 subjects; 1.1 % in the pooled aflibercept 2 mg group, 3 subjects; 1.6% in the brolucizumab 3 mg group in Study B2301).

The severe ocular AEs in the study eye were as follows:

Brolucizumab 6 mg group:

- SOC eye disorders (5 subjects): uveitis (2 subjects), eye irritation (1 subject), iridocyclitis (1 subject), retinal artery occlusion (1 subject), diabetic retinopathy (1 subject)

- SOC infections and infestations (1 subject): endophthalmitis

Aflibercept 2 mg group:

- SOC eye disorders (4 subjects): corneal degeneration (1 subject), retinal detachment (1 subject), cataract (1 subject), diabetic retinopathy (1 subject)

- SOC infections and infestations (1 subject): endophthalmitis

Brolucizumab 3 mg group:

- SOC eye disorders (2 subjects): Uveitis, retinal vasculitis, macular oedema and optic nerve disorder (all 4 events in 1 subject), endophthalmitis and hypopyon (both events in 1 subject), retinal artery occlusion (1 subject)

-Non-ocular AE

The proportion of subjects experiencing at least 1 non-ocular AE was similar between the pooled brolucizumab 6 mg group (49.5%) and pooled aflibercept 2 mg group (51.1%). In Study B2301 at Week 28 the proportion of subjects in the brolucizumab 3 mg group who had at least 1 non-ocular AE was 54.2%. The most frequently reported SOC was infections and infestations (18.2% in the pooled brolucizumab 6 mg group, and 16.0% in the pooled aflibercept 2 mg group; 25.8% in the brolucizumab 3 mg group in Study B2301).

The most frequently reported non-ocular AE by preferred term in any treatment group were hypertension (5.4% of subjects in the pooled brolucizumab 6 mg group, 5.4% of subjects in the pooled aflibercept 2 mg group; 4.7% of subjects in the brolucizumab 3 mg group in Study B2301) and nasopharyngitis (3.8% of subjects in the pooled brolucizumab 6 mg group, 2.7% of subjects in the pooled aflibercept 2 mg group; 6.3% of subjects in the brolucizumab 3 mg group in Study B2301).

CHMP assessment report
EMA/23630/2020 Page 82/125

Table 34: Non-ocular AE in S-db 1

	CRTH258B2301	Pooled	
	28 weeks	28 weeks	28 weeks
Preferred Term	Bro 3mg N=190 n (%)	Bro 6mg N=368 n (%)	Afl 2mg N=368 n (%)
Number of subjects with at least one AE	103 (54.2)	182 (49.5)	188 (51.1)
Hypertension	9 (4.7)	20 (5.4)	20 (5.4)
Nasopharyngitis	12 (6.3)	14 (3.8)	10 (2.7)
Urinary tract infection	9 (4.7)	11 (3.0)	3 (0.8)
Anaemia	2 (1.1)	8 (2.2)	7 (1.9)
Diarrhoea	2 (1.1)	8 (2.2)	6 (1.6)
Influenza	5 (2.6)	6 (1.6)	6 (1.6)
Bronchitis	4 (2.1)	6 (1.6)	5 (1.4)
Upper respiratory tract infection	4 (2.1)	6 (1.6)	2 (0.5)
Diabetes mellitus	4 (2.1)	5 (1.4)	2 (0.5)
Blood pressure increased	4 (2.1)	4 (1.1)	5 (1.4)
Arthralgia	1 (0.5)	4 (1.1)	8 (2.2)

Treatment-related AE

In Loading safety database 1, 1 subject (0.3%) in the pooled brolucizumab 6 mg group and 2 subjects (0.5%) in the pooled aflibercept 2 mg group had non-ocular AEs that were suspected by the Investigator to be related to study drug.

- in the brolucizumab 6 mg group: 1 subject had an AE of blood pressure increased that was suspected to be related to study drug

- in the aflibercept group: 1 subject with lacunar stroke and 1 subject with transient ischemic attack were suspected to be related to study drug

Severity

In Loading database 1, at Week 28, the majority of non-ocular AEs were considered to have a maximum severity which was mild or moderate. The proportion of subjects having mild or moderate non-ocular AEs was 44.0 % in the pooled brolucizumab 6 mg group and 46.0% in the pooled aflibercept 2 mg group. The proportion of subjects with severe non-ocular AEs was similar between treatment groups (20 subjects; 5.4 % in the pooled brolucizumab 6 mg group, 19 subjects; 5.2 % in the pooled aflibercept 2 mg group).

The most frequently reported non-ocular AEs which were considered severe were in the primary SOC of cardiac disorders and the proportion was similar between treatment groups; 7 subjects (1.9%) in the pooled brolucizumab 6 mg group (cardiac failure (3 subjects), myocardial infarction (2 subjects), congestive cardiac failure (1 subject), acute myocardial infarction (1 subject), coronary artery stenosis (1 subject)) and 3 subjects (0.8%) in the pooled aflibercept 2 mg group (cardiac failure (2 subjects), acute myocardial infarction (1 subject)). There were 4 subjects (1.1%) in the pooled brolucizumab group and 3 subjects (0.8%) in the pooled aflibercept 2 mg group, who had severe AEs under the SOC of infections and infestations.

- **52 week S-db**

CHMP assessment report
EMA/23630/2020 Page 83/125

-Ocular AE

In the 52 week safety database the proportion of subjects experiencing at least 1 ocular AE in the study eye was similar between the pooled brolucizumab 6 mg group (35.1%) and pooled aflibercept 2 mg group (34.0%) (Table 35). In Study B2301 the proportion of subjects in the brolucizumab 3 mg group who had at least 1 ocular AE was 42.6%.

Conjunctival hemorrhage was the most commonly reported AE in the 52 week safety database (5.7% of subjects in the pooled brolucizumab 6 mg group, 6.5% of subjects in the pooled aflibercept 2 mg group and 8.9% of subjects in the brolucizumab 3 mg group in Study B2301).

Overall, at Week 52, the incidence of ocular AEs in the study eye was higher in all treatment arms in Study B2301 (brolucizumab 6 mg 40.2%, aflibercept 2 mg 39.0% and brolucizumab 3 mg 42.6%), than in Study B2302 (brolucizumab 6 mg 29.6%, aflibercept 2 mg 28.7%) but the type of AEs and proportion of AEs were similar between treatment arms within each study. However, there were no clinically relevant differences in the incidence of AEs between brolucizumab and aflibercept treatment arms in both pivotal Phase III studies. Thus, comparisons of AE proportions in the brolucizumab 3 mg group of Study B2301 to the pooled brolucizumab 6 mg and aflibercept groups should be made with caution due to this 'study effect'.

Treatment-related AE

The proportion of subjects with ocular AEs in the study eye suspected by the Investigator to be related to study drug was low in both pooled treatment groups of the 52 week S-db (2.7% for the pooled brolucizumab 6 mg group, 1.4% for pooled aflibercept 2 mg group) and in the brolucizumab 3 mg group in Study B2301 (5.3%). There were a small number of AEs reported after Week 28, in both treatment pools, that were suspected by the Investigator to be related to study drug; all AEs were classified in the SOC of Eye disorders in both treatment groups; apart from 1 AE (0.3%) of in the SOC of Investigations (PT of IOP increased in the brolucizumab 6 mg group).

The most frequently reported ocular AE suspected by the Investigator to be related to the study treatment in the 52 week safety database were uveitis 3 subjects (0.8%) in the brolucizumab 6 mg group, 1 subject (0.3%) in the aflibercept group; iridocyclitis; 2 subjects (0.5%) in the brolucizumab 6 mg group, 0 subjects in the aflibercept group and vitreous floaters; 2 subjects (0.5%) in the brolucizumab 6 mg group, 1 subject (0.3%) in the aflibercept group.

Severity

In the 52 week safety database, the majority of ocular AEs in the study eye were considered to have a maximum severity which was mild or moderate. The proportion of subjects having mild or moderate ocular AEs of the study eye was similar across all treatment groups (33.2% in the pooled brolucizumab 6 mg group, 32.1% in the pooled aflibercept 2 mg group and 39.5% in brolucizumab 3 mg group in Study B2301. Seven subjects (1.9 %) in the pooled brolucizumab 6 mg group; 7 subjects (1.9 %) in the pooled aflibercept 2 mg group and 6 subjects (3.2%) in the brolucizumab 3 mg group in Study B2301, had severe ocular AEs in the study eye.

The severe ocular AEs in the study eye for the pooled treatment groups were as follows:

Brolucizumab 6 mg group

- SOC eye disorders (6 subjects): uveitis (2 subjects), eye irritation (1 subject), iridocyclitis (1 subject), retinal artery occlusion (1 subject), diabetic retinopathy (1 subject), diabetic retinal oedema (1 subject)

- SOC infections and infestations (1 subject): endophthalmitis

CHMP assessment report
EMA/23630/2020 Page 84/125

Aflibercept 2 mg group:

- SOC eye disorders (7 subjects): corneal degeneration (1 subject), retinal detachment (2 subjects), cataract (2 subjects), diabetic retinopathy (1 subject), cataract subcapsular (1 subject)

- SOC infections and infestations (1 subject): endophthalmitis

Brolucizumab 3 mg group:

- SOC eye disorders (5 subjects): Uveitis, retinal vasculitis, macular oedema and optic nerve disorder (all 4 events in 1 subject), retinal detachment (1 subject), retinal artery occlusion and retinal vasculitis (both events in 1 subject), retinal vein thrombosis (1 subject) and cystoid macular oedema (1 subject).

- SOC infections and infestations (2 subjects): endophthalmitis (1 subject), endophthalmitis and hypopyon (both events in 1 subject).

Table 35: Ocular AE in 52 week S-db

	CRTH258B2301	Pooled	
Preferred Term	Bro 3mg N=190 n (%)	Bro 6mg N=368 n (%)	Afl 2mg N=368 n (%)
Number of subjects with at least one AE	81 (42.6)	129 (35.1)	125 (34.0)
Conjunctival haemorrhage	17 (8.9)	21 (5.7)	24 (6.5)
Cataract	6 (3.2)	13 (3.5)	14 (3.8)
Dry eye	9 (4.7)	12 (3.3)	10 (2.7)
Vitreous floaters	6 (3.2)	12 (3.3)	7 (1.9)
Eye pain	4 (2.1)	9 (2.4)	6 (1.6)
Vitreous detachment	8 (4.2)	8 (2.2)	2 (0.5)
Conjunctivitis	3 (1.6)	8 (2.2)	1 (0.3)
Diabetic retinal oedema	9 (4.7)	7 (1.9)	5 (1.4)
Intraocular pressure increased	5 (2.6)	7 (1.9)	3 (0.8)
Visual acuity reduced	6 (3.2)	5 (1.4)	9 (2.4)
Retinal exudates	5 (2.6)	4 (1.1)	3 (0.8)
Punctate keratitis	5 (2.6)	3 (0.8)	0
Iridocyclitis	4 (2.1)	3 (0.8)	0
Vision blurred	5 (2.6)	2 (0.5)	4 (1.1)
Conjunctival hyperaemia	4 (2.1)	0	1 (0.3)

At Week 52 the most frequently reported SOC was eye disorders (30.4% of subjects in the pooled brolucizumab 6 mg group, and 30.7% of subjects in the pooled aflibercept 2 mg group; 40.5% of subjects in the brolucizumab 3 mg group in Study B2301).

-Non-ocular AE

In the 52 week safety database, a similar proportion of subjects in the pooled brolucizumab 6 mg group (64.1%), the pooled aflibercept 2 mg group (67.7%) and brolucizumab 3 mg group (64.2%) in Study B2301 experienced at least 1 non-ocular AE (Table 36).

Infections and infestations was the most frequently reported SOC across treatment groups (27.2% of subjects in the pooled brolucizumab 6 mg group, 25.8% of subjects in the pooled aflibercept 2 mg group and 33.2% of subjects in the brolucizumab 3 mg group in Study B2301).

CHMP assessment report
EMA/23630/2020 Page 85/125

Table 36: Non-ocular AE in 52 week S-db

	CRTH258B2301	Pooled	
Preferred Term	Bro 3mg N=190 n (%)	Bro 6mg N=368 n (%)	Afl 2mg N=368 n (%)
Number of subjects with at least one AE	122 (64.2)	236 (64.1)	249 (67.7)
Hypertension	15 (7.9)	30 (8.2)	26 (7.1)
Nasopharyngitis	17 (8.9)	27 (7.3)	25 (6.8)
Urinary tract infection	11 (5.8)	15 (4.1)	10 (2.7)
Headache	2 (1.1)	13 (3.5)	7 (1.9)
Pyrexia	1 (0.5)	12 (3.3)	5 (1.4)
Cough	5 (2.6)	11 (3.0)	13 (3.5)
Bronchitis	4 (2.1)	11 (3.0)	7 (1.9)
Anaemia	3 (1.6)	11 (3.0)	14 (3.8)
Influenza	6 (3.2)	10 (2.7)	7 (1.9)
Upper respiratory tract infection	4 (2.1)	10 (2.7)	4 (1.1)
Diarrhoea	3 (1.6)	9 (2.4)	10 (2.7)
Back pain	1 (0.5)	9 (2.4)	4 (1.1)
Oedema peripheral	2 (1.1)	8 (2.2)	5 (1.4)
Arthralgia	6 (3.2)	6 (1.6)	10 (2.7)
Blood pressure increased	5 (2.6)	6 (1.6)	6 (1.6)
Chronic kidney disease	0	6 (1.6)	8 (2.2)
Diabetes mellitus	5 (2.6)	5 (1.4)	4 (1.1)
Pneumonia	0	5 (1.4)	8 (2.2)
Diabetic nephropathy	2 (1.1)	4 (1.1)	9 (2.4)

The most frequently reported AEs (ocular and non-ocular) in Study B2301 and Study B2302 were consistent with that reported in the 52 week pooled safety database, and were comparable across treatment arms.

Treatment-related AE

In the 52 week safety database there were no further non-ocular AEs which were suspected to be related to study treatment than those observed up to Week 28 (1 subject (0.3%) in the pooled brolucizumab 6 mg group and 2 subjects (0.5%) in the pooled aflibercept 2 mg group had nonocular AEs).

Severity

In the 52 week safety database the majority of non-ocular AEs were considered to have a maximum severity which was mild or moderate. The proportion of subjects having mild or moderate non-ocular AEs was 54.1 % in the pooled brolucizumab 6 mg group and 58.2% in the pooled aflibercept 2 mg group. The proportion of subjects with severe non-ocular AEs was similar between treatment groups (37 subjects; 10.1% in the pooled brolucizumab 6 mg group, 35 subjects; 9.5% in the pooled aflibercept 2 mg group).

The primary SOC with the most frequently reported severe AEs for the 52 week safety database was cardiac disorders; 11 subjects (3.0%) in the pooled brolucizumab 6 mg group (cardiac failure (3 subjects), myocardial infarction (3 subjects), congestive cardiac failure (1 subject), acute myocardial infarction (1 subject), coronary artery stenosis (1 subject), cardiac arrest (1 subject), coronary artery disease (1 subject), aortic valve stenosis (1 subject)) and 7 subjects (1.9%) in the pooled aflibercept 2 mg group (cardiac failure (2 subjects), congestive cardiac failure (1 subject), coronary artery disease (1 subject), acute myocardial infarction (2 subjects), bradycardia (1 subject), cardiorenal syndrome (1 subject), chronic cor pulmonale (1 subject)).

CHMP assessment report
EMA/23630/2020 Page 86/125

There were 6 subjects (1.6%) in the pooled brolucizumab group and 9 subjects (2.4%) in the pooled aflibercept 2 mg group, who had severe AEs under the SOC of nervous system disorders.

2-ANALYSIS OF ADVERSE EFFECT DOSE-RESPONSE INFORMATION

No dedicated analysis was performed to assess the relationship between brolucizumab dose and incidence of AEs.

A comparison of AE event frequencies between the brolucizumab 3 mg and 6 mg groups (dose-response comparison) has to be interpreted with caution since the brolucizumab 3 mg group was only included in Study B2301, while the brolucizumab 6 mg and aflibercept 2 mg results are obtained from the pooled pivotal Study B2301 and Study B2302. Therefore, a direct comparison between brolucizumab 3 mg only in B2301 study and brolucizumab 6 mg in both studies could be confounded by study effect.

In Study B2301, up to Week 52, the overall incidence of ocular and non-ocular AEs and SAEs, and AEs leading to study or treatment discontinuation were generally comparable between the brolucizumab 6 mg and 3 mg arms. The incidence of ocular AEs in the study eye was: brolucizumab 6 mg 40.2%, aflibercept 2 mg 39.0% and brolucizumab 3 mg 42.6%). Fewer AESIs were reported in the brolucizumab 6 mg arm compared to the brolucizumab 3 mg arm.

Serious adverse events and deaths, other significant events

1- DEATHS

Overall, 13 subjects died during the 52 week primary analysis of Study B2301 and Study B2302; all deaths were not suspected to be related to study treatment by the investigator. The deaths occurred in 8 subjects in pooled brolucizumab 6 mg group, 4 subjects in the pooled aflibercept 2 mg group and 1 subject in the brolucizumab 3 mg group in Study B2301.

- **Loading s-db 1 and 2**

In the Loading safety database 1, 3 subjects (0.8%) in the pooled brolucizumab 6 mg group, 2 subjects (0.5%) in the pooled aflibercept 2 mg group and 1 subject (0.5%) in the brolucizumab 3 mg group in Study B2301 died up to and including Week 28 (Table 37).

None of the deaths were suspected to be related to study drug by the Investigator.

CHMP assessment report
EMA/23630/2020 Page 87/125

Table 37: Deaths reported in loading S-db 1

	CRTH258B2301	Pooled	
	28 weeks	28 weeks	28 weeks
Primary system organ class Preferred term	Bro 3mg N=190 n (%)	Bro 6mg N=368 n (%)	Afl 2mg N=368 n (%)
Number of deaths	1 (0.5)	3 (0.8)	2 (0.5)
General disorders and administration site conditions	0	1 (0.3)	0
Sudden death	0	1 (0.3)	0
Infections and infestations	1 (0.5)	1 (0.3)	0
Sepsis	0	1 (0.3)	0
Pneumonia fungal	1 (0.5)	0	0
Nervous system disorders	0	0	1 (0.3)
Hypoglycaemic coma	0	0	1 (0.3)
Respiratory, thoracic and mediastinal disorders	0	1 (0.3)	1 (0.3)
Pulmonary oedema	0	1 (0.3)	0
Respiratory failure	0	0	1 (0.3)

- **52 week S-db**

In the 52 week safety database, 8 subjects (2.2%) in the pooled brolucizumab 6 mg group including 1 subject who died due to COVID-19 infection, 4 subjects (1.1%) in the pooled aflibercept 2 mg group and 1 subject (0.5%) in the brolucizumab 3 mg group in Study B2301 died up to and including Week 52 (Table 38).

None of the deaths were suspected to be related to study drug by the Investigator.

Table 38: Deaths reported in 52-week S-db

	CRTH258B2301	Pooled	
Primary system organ class Preferred term	Bro 3mg N=190 n (%)	Bro 6mg N=368 n (%)	Afl 2mg N=368 n (%)
Number of deaths	1 (0.5)	8 (2.2)	4 (1.1)
Cardiac disorders	0	1 (0.3)	0
Cardiac arrest	0	1 (0.3)	0
General disorders and administration site conditions	0	2 (0.5)	0
Death	0	1 (0.3)	0
Sudden death	0	1 (0.3)	0
Infections and infestations	1 (0.5)	2 (0.5)	0
COVID-19	0	1 (0.3)	0
Sepsis	0	1 (0.3)	0
Pneumonia fungal	1 (0.5)	0	0
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	0	2 (0.5)	1 (0.3)
Brain neoplasm	0	1 (0.3)	0
Pancreatic carcinoma	0	1 (0.3)	0
Bronchial carcinoma	0	0	1 (0.3)
Nervous system disorders	0	0	2 (0.5)
Cerebral haemorrhage	0	0	1 (0.3)
Hypoglycaemic coma	0	0	1 (0.3)
Respiratory, thoracic and mediastinal disorders	0	1 (0.3)	1 (0.3)

CHMP assessment report
EMA/23630/2020 Page 88/125

Pulmonary oedema	0	1 (0.3)	0
Respiratory failure	0	0	1 (0.3)

2- Other serious AE

- **Loading S-db 1 and 2**

-Ocular AE

In the Loading safety database 1 & 2, at Week 28, 4 subjects (1.1%) in the pooled brolucizumab 6 mg group, 3 subjects (0.8%) in the pooled aflibercept 2 mg group and 5 subjects (2.6%) in the brolucizumab 3 mg group in Study B2301 experienced at least 1 ocular SAE (Table 39). The most frequently reported SOC across treatment groups was eye disorders, which occurred in 3 subjects (0.8%) in the pooled brolucizumab 6 mg group, 2 subjects (0.5%) in the pooled aflibercept 2 mg group and 4 subjects (2.1%) in the brolucizumab 3 mg group in Study B2301.

Each SAE was reported only once in Loading safety database 1 & 2 (at Week 28) apart from the SAEs with PTs of retinal vasculitis and endophthalmitis. Retinal vasculitis was reported in 2 subjects (1.1%) in the brolucizumab 3 mg group in Study B2301 but in 0 subject in the pooled brolucizumab 6 mg group and 0 subject in the pooled aflibercept 2 mg group. Endophthalmitis was reported in 2 subjects (0.5%) in the pooled aflibercept 2 mg group, 1 subject (0.3%) in the pooled brolucizumab 6 mg group and 1 subject (0.5%) in the brolucizumab 3 mg group in Study B2301 (Table 39).

Table 39: Ocular SAE reported in the loading S-db 1&2

	CRTH258B2301	Pooled		
	28 weeks	28 weeks	28 weeks	20 weeks
Primary System Organ Class Preferred Term	Bro 3mg N=190 n (%)	Bro 6mg N=368 n (%)	Afl 2mg N=368 n (%)	Afl 2mg N=368 n (%)
Number of subjects with at least one SAE	5 (2.6)	4 (1.1)	3 (0.8)	2 (0.5)
Eye disorders	4 (2.1)	3 (0.8)	2 (0.5)	1 (0.3)
Uveitis	1 (0.5)	1 (0.3)	0	0
Conjunctival cyst	0	1 (0.3)	0	0
Pterygium	0	1 (0.3)	0	0
Retinal artery occlusion	0	1 (0.3)	0	0
Retinal vasculitis	2 (1.1)	0	0	0
Glaucoma	1 (0.5)	0	0	0
Macular fibrosis	1 (0.5)	0	0	0
Macular oedema	1 (0.5)	0	0	0
Optic nerve disorder	1 (0.5)	0	0	0
Cataract	0	0	1 (0.3)	0
Retinal detachment	0	0	1 (0.3)	1 (0.3)
Infections and infestations	1 (0.5)	1 (0.3)	2 (0.5)	2 (0.5)
Endophthalmitis	1 (0.5)	1 (0.3)	2 (0.5)	2 (0.5)

-Non-ocular AE

In the Loading safety database 1, a similar proportion of subjects across treatment groups experienced at least 1 non-ocular SAE; 10.3% in the pooled brolucizumab 6 mg group, 12.5% in the pooled aflibercept 2 mg group and 8.4% in the brolucizumab 3 mg group in Study B2301 (Table 40).

The most frequently reported non-ocular SAE by preferred term in the pooled brolucizumab 6 mg group (3 subjects; 0.8%) was diabetes mellitus; there were 0 subject where this SAE had been reported in the

CHMP assessment report
EMA/23630/2020 Page 89/125

pooled aflibercept 2 mg group, or brolucizumab 3 mg group in Study B2301 (Table 40). Myocardial infarction was reported in 2 subjects (0.5%) in the pooled brolucizumab 6 mg group, 1 subject (0.5%) in the brolucizumab 3 mg group in Study B2301 and 0 subject in the pooled aflibercept 2 mg group. Cardiac failure congestive was reported in 2 subjects (1.1%) in the brolucizumab 3 mg group in Study B2301, 1 subject (0.3%) in the pooled brolucizumab 6 mg group and 0 subject in the pooled aflibercept 2 mg group.

Table 40: Non-ocular SAE reported in the loading S-db 1

	CRTH258B2301	Pooled	
	28 weeks	28 weeks	28 weeks
Preferred Term	Bro 3mg N=190 n (%)	Bro 6mg N=368 n (%)	Afl 2mg N=368 n (%)
Number of subjects with at least one SAE	16 (8.4)	38 (10.3)	46 (12.5)
Diabetes mellitus	0	3 (0.8)	0
Myocardial infarction	1 (0.5)	2 (0.5)	0
Gangrene	0	2 (0.5)	1 (0.3)
Hypertensive crisis	0	2 (0.5)	1 (0.3)
Orthostatic hypotension	0	2 (0.5)	0
Cardiac failure congestive	2 (1.1)	1 (0.3)	0
Cerebrovascular accident	1 (0.5)	1 (0.3)	1 (0.3)
Sepsis	1 (0.5)	1 (0.3)	1 (0.3)
Hypertension	1 (0.5)	1 (0.3)	0
Cardiac failure	0	1 (0.3)	4 (1.1)
Pneumonia	0	1 (0.3)	4 (1.1)
Angina pectoris	1 (0.5)	0	0
Arrhythmia	1 (0.5)	0	0
Atrioventricular block	1 (0.5)	0	0
Benign prostatic hyperplasia	1 (0.5)	0	0
Cardiac arrest	1 (0.5)	0	0
Cerebral haemorrhage	1 (0.5)	0	0
Colon cancer	1 (0.5)	0	0
Diabetic foot infection	1 (0.5)	0	0
Diabetic nephropathy	1 (0.5)	0	0
Gas gangrene	1 (0.5)	0	0
Haematemesis	1 (0.5)	0	0
Inguinal hernia	1 (0.5)	0	0
International normalised ratio increased	1 (0.5)	0	0
Pneumonia fungal	1 (0.5)	0	0
Pyrexia	1 (0.5)	0	0
Skin flap necrosis	1 (0.5)	0	0
Renal failure	0	0	3 (0.8)
Osteomyelitis	0	0	2 (0.5)
Urinary retention	0	0	2 (0.5)

- **52 week S-db**

-Ocular AE

In the 52 week safety database, the frequency of ocular serious adverse events was low and consistent across all three treatment groups (Table 41). A higher proportion of subjects (3.7%) in the brolucizumab 3 mg group in Study B2301 experienced at least 1 SAE in the study eye compared to the pooled brolucizumab 6 mg group (1.6%) and the pooled aflibercept 2 mg group (1.9%); however this could be

CHMP assessment report
EMA/23630/2020 Page 90/125

a study effect. The most frequently reported SOC across treatment groups in the 52 week safety database was eye disorders (4 subjects (1.1%) in the pooled brolucizumab 6 mg group, 6 subjects (1.6%) in the pooled aflibercept 2 mg group and 6 subjects (3.2%) in the brolucizumab 3 mg group in Study B2301 experienced at least 1 ocular SAE).

The most frequently reported SAEs in the study eye by preferred term were retinal vasculitis and cataract. Retinal vasculitis was reported in 3 subjects (1.6%) in the brolucizumab 3 mg group in Study B2301 and 0 subjects in the pooled brolucizumab 6 mg group and pooled aflibercept 2 mg groups (Table 41). Cataract was reported as an SAE in 3 subjects (0.8%) in the pooled aflibercept 2 mg group and 0 subjects in the pooled brolucizumab 6 mg group and brolucizumab 3 mg group in Study B2301.

Frequencies of ocular SAEs were low for the study eye and the fellow eye.

Table 41: Ocular SAE reported in the week 52 S-db

	CRTH258B2301	Pooled	
Primary System Organ Class Preferred Term	Bro 3mg N=190 n (%)	Bro 6mg N=368 n (%)	Afl 2mg N=368 n (%)
Number of subjects with at least one SAE	7 (3.7)	6 (1.6)	7 (1.9)
Eye disorders	6 (3.2)	4 (1.1)	6 (1.6)
Uveitis	1 (0.5)	1 (0.3)	1 (0.3)
Glaucoma	1 (0.5)	1 (0.3)	0
Conjunctival cyst	0	1 (0.3)	0
Diabetic retinal oedema	0	1 (0.3)	0
Pterygium	0	1 (0.3)	0
Retinal artery occlusion	0	1 (0.3)	0
Vitreous floaters	0	1 (0.3)	0
Retinal vasculitis	3 (1.6)	0	0
Retinal detachment	1 (0.5)	0	2 (0.5)
Macular fibrosis	1 (0.5)	0	0
Macular oedema	1 (0.5)	0	0
Optic nerve disorder	1 (0.5)	0	0
Retinal vein thrombosis	1 (0.5)	0	0
Vitritis	1 (0.5)	0	0
Cataract	0	0	3 (0.8)
Retinal tear	0	0	1 (0.3)
Infections and infestations	2 (1.1)	2 (0.5)	2 (0.5)
Endophthalmitis	2 (1.1)	1 (0.3)	2 (0.5)
Ophthalmic herpes zoster	0	1 (0.3)	0

-Non-ocular AE

In the 52 week safety database, a similar proportion of subjects across treatment groups experienced at least 1 non-ocular SAE (17.7% in the pooled brolucizumab 6 mg group, 20.1% in the pooled aflibercept 2 mg group and 12.1% in the brolucizumab 3 mg group in Study B2301 (Table 42).

The most frequently reported non-ocular SAE by preferred term in the pooled brolucizumab 6 mg group was myocardial infarction which was reported in 3 subjects (0.8%), 1 subject (0.5%) in the brolucizumab 3 mg group in Study B2301 and 1 subject (0.3%) in the pooled aflibercept 2 mg group. Diabetes mellitus was reported in the pooled brolucizumab 6 mg group in 3 subjects (0.8%) with 0 subjects reporting this SAE in the pooled aflibercept 2 mg group or brolucizumab 3 mg group in Study B2301. Congestive cardiac failure was reported in subjects (1.1%) in the brolucizumab 3 mg group in Study B2301, 2

CHMP assessment report
EMA/23630/2020 Page 91/125

subjects (0.5%) in the pooled brolucizumab 6 mg group and 1 subject (0.3%) in the pooled aflibercept 2 mg group.

Non-ocular SAEs up to Week 52 in Study B2301 and Study B2302 are detailed in Section 12.3.2.2 of each individual CSR.

Table 42: Non-ocular SAE reported in the week 52 S-db

	CRTH258B2301	Pooled	
Preferred Term	Bro 3mg N=190 n (%)	Bro 6mg N=368 n (%)	Afl 2mg N=368 n (%)
Number of subjects with at least one SAE	23 (12.1)	65 (17.7)	74 (20.1)
Myocardial infarction	1 (0.5)	3 (0.8)	1 (0.3)
Diabetes mellitus	0	3 (0.8)	0
Cardiac failure congestive	2 (1.1)	2 (0.5)	1 (0.3)
Pneumonia	0	2 (0.5)	4 (1.1)
Anaemia	0	2 (0.5)	2 (0.5)
Coronary artery stenosis	0	2 (0.5)	1 (0.3)
Gangrene	0	2 (0.5)	1 (0.3)
Hypertensive crisis	0	2 (0.5)	1 (0.3)
Respiratory failure	0	2 (0.5)	1 (0.3)
Orthostatic hypotension	0	2 (0.5)	0
Pancreatic carcinoma	0	2 (0.5)	0
Subdural haematoma	0	2 (0.5)	0
Cellulitis	1 (0.5)	1 (0.3)	2 (0.5)
Cerebrovascular accident	1 (0.5)	1 (0.3)	2 (0.5)
Sepsis	1 (0.5)	1 (0.3)	1 (0.3)
Acute kidney injury	1 (0.5)	1 (0.3)	0
Cardiac arrest	1 (0.5)	1 (0.3)	0
Chronic obstructive pulmonary disease	1 (0.5)	1 (0.3)	0
Colon cancer	1 (0.5)	1 (0.3)	0
Hypertension	1 (0.5)	1 (0.3)	0
Cardiac failure	0	1 (0.3)	4 (1.1)
Renal failure	0	1 (0.3)	4 (1.1)
Coronary artery disease	0	1 (0.3)	3 (0.8)
Acute myocardial infarction	0	1 (0.3)	2 (0.5)
Atrial fibrillation	0	1 (0.3)	2 (0.5)
Chronic kidney disease	0	1 (0.3)	2 (0.5)
Extremity necrosis	0	1 (0.3)	2 (0.5)
Diabetic nephropathy	1 (0.5)	0	2 (0.5)
Angina pectoris	1 (0.5)	0	1 (0.3)
Cerebral haemorrhage	1 (0.5)	0	1 (0.3)

CHMP assessment report
EMA/23630/2020 Page 92/125

Arrhythmia	1 (0.5)	0	0
Atrioventricular block	1 (0.5)	0	0
Benign prostatic hyperplasia	1 (0.5)	0	0
Chest pain	1 (0.5)	0	0
Dehydration	1 (0.5)	0	0
Diabetic foot infection	1 (0.5)	0	0
Gas gangrene	1 (0.5)	0	0
Haematemesis	1 (0.5)	0	0
Hypoglycaemia	1 (0.5)	0	0
Inguinal hernia	1 (0.5)	0	0
International normalised ratio increased	1 (0.5)	0	0
Osteomyelitis acute	1 (0.5)	0	0
Peripheral arterial occlusive disease	1 (0.5)	0	0
Pneumonia fungal	1 (0.5)	0	0
Pulmonary sepsis	1 (0.5)	0	0
Pyrexia	1 (0.5)	0	0
Skin flap necrosis	1 (0.5)	0	0
Ulna fracture	1 (0.5)	0	0
Asthma	0	0	2 (0.5)
Cholelithiasis	0	0	2 (0.5)
Diarrhoea	0	0	2 (0.5)
Goitre	0	0	2 (0.5)
Osteomyelitis	0	0	2 (0.5)
Urinary retention	0	0	2 (0.5)

Study B2304 and Study B2305

For Study B2304 and Study B2305 SAE cases were retrieved from their respective study starts (Study B2304: FPFV 23-Aug-2019, Study B2305: FPFV 17-Jul-2019) until 15-Jan-2021.

At the time of the safety data cut-off (15-Jan-2021) for Study B2304, 17% of enrollment had completed (46 subjects had been randomized/ 268 planned subjects) and for Study B2305 enrollment had been completed; 517/ 517 subjects had been randomized.

No new safety signal for brolucizumab was identified from a review of these SAE cases in the ongoing DME studies. The SAEs identified in the ongoing DME studies were similar to the safety data observed in the CSRs for Study B2301 and Study B2302.

AESI

1-OCULAR AESI

- **Loading S-db 1**

A total of 19 subjects in the Loading safety database 1 had at least one ocular AESI in the study eye. The percentage of subjects with at least one event categorized under endophthalmitis was similar (0.3% (95% CI 0.01%-1.50%) in the pooled brolucizumab 6 mg group vs. 0.5% (95% CI 0.07%-1.95%) in the pooled aflibercept 2 mg group, with a risk difference for pooled brolucizumab 6 mg – pooled aflibercept 2 mg of -0.3% (95% CI -7.62%-7.08%). One subject (0.5%) in the brolucizumab 3 mg group in Study B2301 had an event categorized as endophthalmitis.

The percentage of subjects with at least one event categorized under intraocular inflammation was higher in the pooled brolucizumab 6 mg group 1.6% (95% CI 0.53%-2.99%) vs. 0.5% (95% CI 0.00-1.66%)

CHMP assessment report
EMA/23630/2020 Page 93/125

in the pooled aflibercept 2 mg group, with a risk difference for pooled brolucizumab 6 mg – pooled aflibercept 2 mg of 1.1% (95% CI -0.54%-2.72%). There were 3.7% of subjects who had events categorized as intraocular inflammation in the brolucizumab 3 mg group in Study B2301.

There are many PTs under the category term of intraocular (only retinal vasculitis is displayed separately in Table 43). There was 1 subject (0.3%) with at least one event categorized under the PT of retinal vasculitis in the pooled brolucizumab 6 mg group (95% CI 0.01%-1.50%) vs. 0 subjects (95% CI 0-1.0%) in the pooled aflibercept 2 mg group, with a risk difference for pooled brolucizumab 6 mg – pooled aflibercept 2 mg of 0.3% (95% CI -7.08%-7.62%). There were 2 subjects (1.1%) who had events with a PT of retinal vasculitis in the brolucizumab 3 mg group in Study B2301.

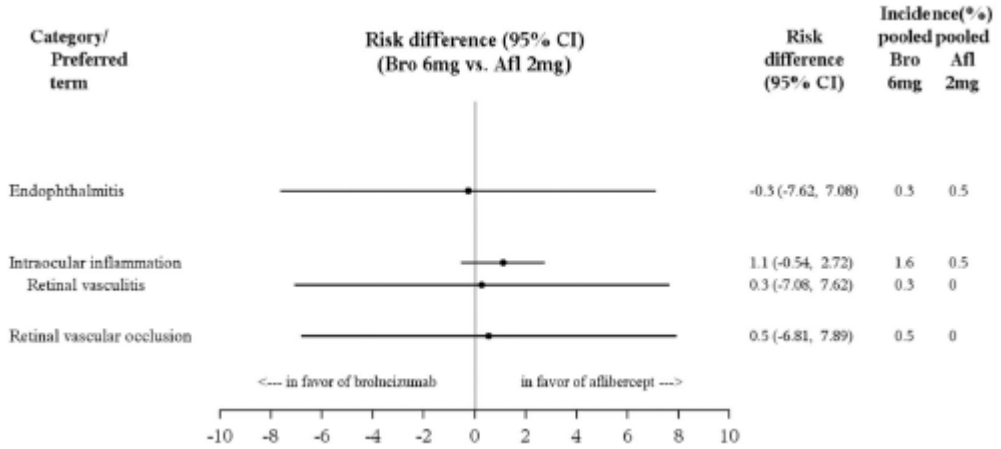
There were 2 subjects with at least one event categorized under retinal vascular occlusion in the pooled brolucizumab 6 mg group 0.5% (95% CI 0.07%-1.95%) vs. 0% (95% CI 0.00-1.00%)) in the pooled aflibercept 2 mg group, with a risk difference for pooled brolucizumab 6 mg – pooled aflibercept 2 mg of 0.5% (95% CI -6.81%-7.89%). One subject (0.5%) in the brolucizumab 3 mg group in Study B2301 had an event categorized as retinal vascular occlusion.

Table 43: Ocular AESI in the loading phase (S-db 1)

		CRTH258B2301	Pooled	
			28 weeks	
Category Preferred term	Measurement	Bro 3mg N=190	Bro 6mg N=368	Afl 2mg N=368
Number of subjects with at least one AE of special interest	n (%) [E]	7 (3.7)[13]	8 (2.2)[12]	4 (1.1)[5]
Endophthalmitis	n (%) (95% CI) [E]	1 (0.5)[1]	1 (0.3) (0.01,1.50)[1]	2 (0.5) (0.07,1.95)[2]
	RD Wk 28 (95% CI)		-0.3 (-7.62, 7.08)	
Intraocular inflammation	n (%) (95% CI) [E]	7 (3.7)[11]	6 (1.6) (0.53,2.99)[9]	2 (0.5) (0.00,1.66)[3]
	RD Wk 28 (95% CI)		1.1 (-0.54,2.72)	
Retinal vasculitis *	n (%) (95% CI) [E]	2 (1.1)[2]	1 (0.3) (0.01,1.50)[1]	0 (0.0) (0.00,1.00)[0]
	RD Wk 28 (95% CI)		0.3 (-7.08, 7.62)	
Retinal vascular occlusion	n (%) (95% CI) [E]	1 (0.5)[1]	2 (0.5) (0.07,1.95)[2]	0 (0.0) (0.00,1.00)[0]
	RD Wk 28 (95% CI)		0.5 (-6.81, 7.89)	

CHMP assessment report
EMA/23630/2020 Page 94/125

Table 44: Forest plot for AESI including incidences and risk differences for pooled brolucizumab 6 mg vs. pooled aflibercept 2 mg, by category (S-db 1)



- **52 weeks S-db**

A total of 29 subjects in the 52 week safety database had at least one ocular AESI in the study eye up to Week 52. Since there were a total 19 subjects who had ocular AESIs up to Week 28, the majority of subjects (19/29; 66%) had their first ocular AESI in the first 28 weeks (approximately 6 months) of treatment.

There were no further cases of endophthalmitis occurring in subjects after 28 weeks treatment in the pooled brolucizumab 6 mg group and pooled aflibercept 2 mg groups (0.3% (95% CI 0.01%-1.50%) in the brolucizumab 6 mg group vs. 0.5% (95% CI 0.07%-1.95%) in the aflibercept group, with a risk difference for pooled brolucizumab 6 mg – pooled aflibercept 2 mg of -0.3% (95% CI -7.62%-7.08%).

In the week 52 safety database the percentage of subjects with at least one event categorized under endophthalmitis was the same as at Week 28 and similar (0.3% (95% CI 0.01%-1.50%) in the pooled brolucizumab 6 mg group vs. 0.5% (95% CI 0.07%-1.95%) in the pooled aflibercept 2 mg group, with a risk difference for pooled brolucizumab 6 mg – pooled aflibercept 2 mg of -0.3% (95% CI -7.62%-7.08%). There was 1 additional subject who had endophthalmitis after 28 weeks treatment; so a total of 2 subjects (1.1%) in the brolucizumab 3 mg group in Study B2301 in the week 52 safety database.

In the 52 week safety database the percentage of subjects with at least one event categorized under intraocular inflammation was higher in the pooled brolucizumab 6 mg group (13 events in 10 subjects; 2.7% (95% CI 0.84%-5.29%) vs. 1.1% (5 events in 4 subjects; 95% CI 0.00- 2.49%) in the pooled aflibercept 2 mg group, with a risk difference for pooled brolucizumab 6 mg – pooled aflibercept 2 mg of 1.6% (95% CI -0.83%-4.76%). Nine subjects (4.7%) in the brolucizumab 3 mg group in Study B2301 had 17 events categorized as intraocular inflammation.

In the 52 week safety database there was 1 subject (0.3%) with at least one event categorized under the PT of retinal vasculitis in the pooled brolucizumab 6 mg group (95% CI 0.01%-1.50%) vs. 0 subjects (95% CI 0-1.0%) in the pooled aflibercept 2 mg group, with a risk difference for pooled brolucizumab 6 mg – pooled aflibercept 2 mg of 0.3% (95% CI -7.08%-7.62%). In the brolucizumab 3 mg treatment group in Study B2301 there was one additional subject with an event with a PT of retinal vasculitis; thus a total of 3 subjects (1.6%) at Week 52 (Table 2-20).

In the 52 week safety database there was 1 additional event categorized under retinal vascular occlusion in the pooled brolucizumab 6 mg group; total of 2 subjects (0.5% (95% CI 0.07%- 1.95%) and 1 subject (0.3% (95% CI 0.01%-1.50%)) in the pooled aflibercept 2 mg group, with a risk difference for pooled brolucizumab 6 mg – pooled aflibercept 2 mg of 0.3% (95% CI - 7.08%-7.62%). There was 1 additional

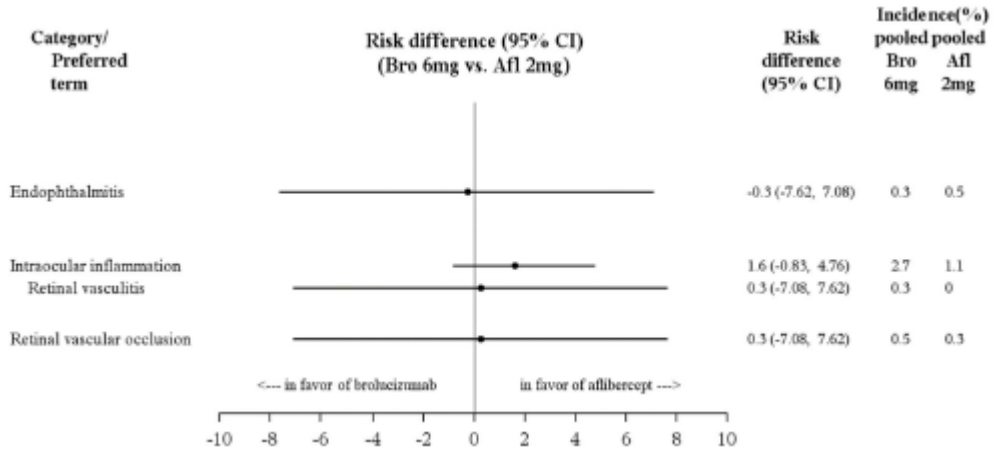
CHMP assessment report
EMA/23630/2020 Page 95/125

event categorized under retinal vascular occlusion in the brolucizumab 3 mg group in Study B2301; total of 2 subjects (1.1%) in the week 52 safety database.

Table 45: Ocular AESI in the maintenance phase (S-db 3)

Category Preferred term	Measurement	CRTH258B2301 Bro 3mg N=190	Pooled Bro 6mg N=368	Pooled Afl 2mg N=368
Number of subjects with at least one AE of special interest	n (%) [E]	10 (5.3)[21]	12 (3.3)[16]	7 (1.9)[8]
Endophthalmitis	n (%) (95% CI) [E]	2 (1.1)[2]	1 (0.3) (0.01,1.50)[1]	2 (0.5) (0.07,1.95)[2]
	RD Wk 52 (95% CI)		-0.3 (-7.62, 7.08)	
Intraocular inflammation	n (%) (95% CI) [E]	9 (4.7)[17]	10 (2.7) (0.84,5.29)[13]	4 (1.1) (0.00,2.49)[5]
	RD Wk 52 (95% CI)		1.6 (-0.83,4.76)	
Retinal vasculitis *	n (%) (95% CI) [E]	3 (1.6)[3]	1 (0.3) (0.01,1.50)[1]	0 (0.0) (0.00,1.00)[0]
	RD Wk 52 (95% CI)		0.3 (-7.08, 7.62)	
Retinal vascular occlusion	n (%) (95% CI) [E]	2 (1.1)[2]	2 (0.5) (0.07,1.95)[2]	1 (0.3) (0.01,1.50)[1]
	RD Wk 52 (95% CI)		0.3 (-7.08, 7.62)	

Table 46: Forest plot for AESI including incidences and risk differences for pooled brolucizumab 6 mg vs. pooled aflibercept 2 mg, by category (S-db 3)



At Week 52, there were more ocular AEs of special interest reported in Study B2301 compared to Study B2302 (Table 47). Intraocular inflammation was reported in more subjects in the brolucizumab 6 mg (7 subjects; 3.7%) and 3 mg (9 subjects; 4.7%) treatment groups in Study B2301 compared to the 6 mg brolucizumab (3 subjects; 1.7%) treatment group in Study B2302.

There were no reports of AEs categorized with a PT of retinal vasculitis in Study B2302 (in either the brolucizumab 6 mg group or the aflibercept 2 mg group). However, in Study B2301 in the brolucizumab groups there were 3 subjects (1.6%) in the brolucizumab 3 mg treatment group and 1 subject (0.5%) in the brolucizumab 6 mg treatment group (and 0 subjects in the aflibercept 2 mg treatment group) with

CHMP assessment report
EMA/23630/2020 Page 96/125

AEs categorized with a PT of retinal vasculitis. There was 1 subject (0.6%) who had an AE categorized as retinal vascular occlusion in the brolucizumab 6 mg group and 1 subject (0.6%) who had an AE categorized as retinal vascular occlusion in the aflibercept 2 mg treatment group in Study B2302. However, in Study B2301 in the brolucizumab groups there were 2 subjects (1.1%) in the brolucizumab 3 mg group and 1 subject (0.5%) who had an AE categorized as retinal vascular occlusion (and 0 subjects in the aflibercept 2 mg group).

Table 47: Ocular AESI for the study eye in Study B2301 and Study B2302 (52 week S-db)

	CRTH2582301			CRTH2582302	
	Bro 3mg N=190	Bro 6mg N=189	Afl 2mg N=187	Bro 6mg N=179	Afl 2mg N=181
Category	n (%)	n (%)	n (%)	n (%)	n (%)
Number of subjects with at least one AE of special interest	10 (5.3)	7 (3.7)	2 (1.1)	5 (2.8)	5 (2.8)
Endophthalmitis	2 (1.1)	0	1 (0.5)	1 (0.6)	1 (0.6)
Intraocular inflammation *	9 (4.7)	7 (3.7)	1 (0.5)	3 (1.7)	3 (1.7)
Retinal Vasculitis *	3 (1.6)	1 (0.5)	0	0	0
Retinal vascular occlusion	2 (1.1)	1 (0.5)	0	1 (0.6)	1 (0.6)

Adverse events categorized under intraocular inflammation including retinal vasculitis

In the 52 week safety database the percentage of subjects with at least 1 event categorized under intraocular inflammation was higher in the pooled brolucizumab 6 mg group (2.7%) than in the pooled aflibercept 2 mg group (1.1%) with a risk difference of 1.6% (95% CI: −0.83-4.76). 4.7% of subjects in the brolucizumab 3 mg group of Study B2301 had an event of intraocular inflammation. The PTs for the AEs which were reported under the category intraocular inflammation for the pooled brolucizumab 6 group were uveitis, iridocyclitis, retinal vasculitis, iritis and eye inflammation.

There were a total of 13 events in the pooled brolucizumab 6 mg group, 5 events in the pooled aflibercept 2 mg group, and 17 events in the brolucizumab 3 mg group of Study B2301. Most events of intraocular inflammation were mild or moderate in severity (10/13 in the brolucizumab 6 mg group, 5/5 in the aflibercept group, and 13/17 in the brolucizumab 3 mg group of Study B2301).

There was a difference between the overall incidence of events categorized under intraocular inflammation between Study B2301 and Study B2302, for brolucizumab 6 mg treatment group and aflibercept 2 mg treatment group at Week 52 (B2301: 3.7% vs. 0.5% for brolucizumab 6 mg vs. aflibercept, respectively; B2302: 1.7% vs. 1.7% for brolucizumab 6 mg vs. aflibercept, respectively).

The majority of the subjects in the brolucizumab groups with at least 1 event categorized under intraocular inflammation experienced the event within 28 weeks of starting treatment (6/10 subjects in the brolucizumab 6 mg group, 2/4 subjects in the pooled aflibercept group, and 7/9 subjects in the brolucizumab 3 mg group of Study B2301).

Retinal vasculitis

In the 52 week safety database all subjects who had at least 1 event categorized under the PT of retinal vasculitis were in Study B2301. There was 1 subject (0.3%) in the pooled brolucizumab 6 mg group vs. 0 subjects in the pooled aflibercept 2 mg group, risk difference for pooled brolucizumab 6 mg – pooled aflibercept 2 mg of 0.3% (95% CI -7.08%-7.62%). In the brolucizumab 3 mg treatment group there were 3 subjects (1.6%) with a PT of retinal vasculitis.

CHMP assessment report
EMA/23630/2020 Page 97/125

Most of the subjects in the brolucizumab groups with at least 1 event categorized under the PT of retinal vasculitis experienced the event within 28 weeks of starting treatment (1/1 subject in the pooled brolucizumab 6 mg group and 2/3 subjects in the brolucizumab 3 mg group of Study B2301).

Adverse events categorized as retinal vascular occlusion

The number of subjects with at least 1 event categorized as retinal vascular occlusion in the 52 week safety database was low: 2 subjects (0.5%) in the pooled brolucizumab 6 mg group, 1 subject (0.3%) in the pooled aflibercept 2 mg group, and 2 subjects (1.1%) in the brolucizumab 3 mg group of Study B2301.

Each event of retinal vascular occlusion only occurred once for each subject. Four of 5 events were considered to have been suspected to be related to the study treatment by the investigator; 1 event in the brolucizumab 6 mg group was not suspected to be related to study treatment or the IVT injection procedure by the investigator. Three of the 5 events (2 in the pooled brolucizumab 6 mg group and 1 in the brolucizumab 3 mg group of Study B2301) occurred within the first 28 weeks of starting treatment.

One subject in the brolucizumab 6 mg treatment group in Study B2302 had significant vision loss (BCVA score of 0 letters on Day 115; score was 75 letters at baseline). This decrease in visual acuity was reported in parallel to the retinal artery occlusion (serious event with reported term of "central retinal artery occlusion"). On the same day, the subject discontinued from the study due to the SAE. This subject had retinal vascular disorder in their medical history and this may have contributed to the event of (central) retinal artery occlusion. The investigator assessed the event (retinal artery occlusion) as not suspected to be related to the study medication and/or injection procedure.

Adverse events categorized under endophthalmitis

The number of subjects with at least one event categorized under endophthalmitis in the 52 week safety database was low and in all but 1 subject occurred in the first 28 weeks of treatment. Five subjects in total had single events of endophthalmitis: 1 subject (0.3%) in the pooled brolucizumab 6 mg group, 2 subjects (0.5%) in the aflibercept group, and 2 subjects (1.1%) in the brolucizumab 3 mg group of Study B2301. The risk difference between brolucizumab 6 mg and aflibercept was −0.3 (95% CI: −7.62-7.08). All AEs categorized as endophthalmitis were reported as serious. Two events were considered to have been related to the IVT injection procedure by the investigator (1 in the aflibercept 2 mg group and 1 in the brolucizumab 3 mg group of Study B2301; both had positive bacterial cultures: Staphylococcus epidermidis and Streptococcus), 1 event was considered to have been related to the study treatment by the investigator (in the brolucizumab 3 mg group of Study B2301; culture test was negative), and 2 events were not suspected to have been related to study treatment or IVT injection procedure by the investigator (1 event in the aflibercept 2 mg group (culture positive for Acinetobacter baumannii) and 1 event in the brolucizumab 6 mg group (culture negative)).

2-OTHER AESI

- **Loading S-db 1**

The percentage of subjects with at least one event categorized under the other safety topics of interest of hypertension, non-ocular hemorrhage, retinal detachment and retinal tear and venous thromboembolic events were similar in the pooled brolucizumab 6 mg and pooled aflibercept 2 mg group at Week 28.

There were more subjects who had events categorized as ocular arterial thromboembolic events in the pooled brolucizumab 6 mg group (0.8%; 95% CI 0.17%-2.36%) vs. 0% (95% CI 0-1.00%) compared to the pooled aflibercept 2 mg group. More events categorized as non-ocular arterial thromboembolic

CHMP assessment report
EMA/23630/2020 Page 98/125

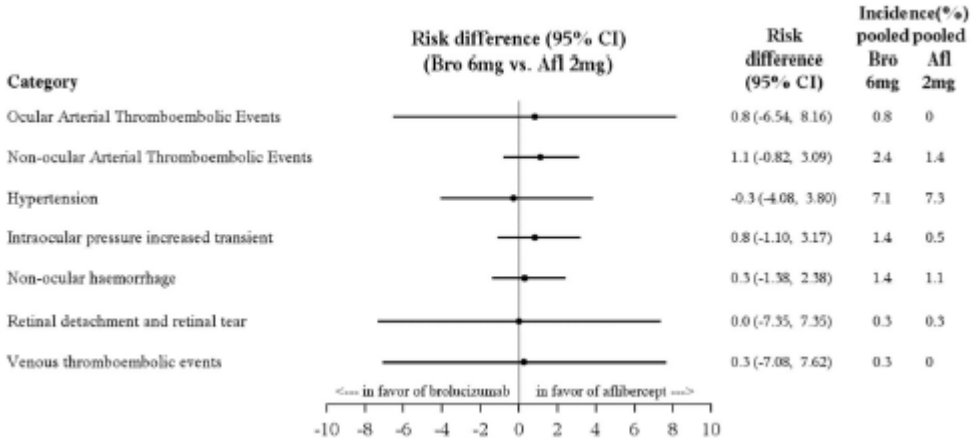
events were reported in subjects in the pooled brolucizumab 6 mg group: 2.4% (95% CI 1.06%-4.23%) compared to the pooled aflibercept 2 mg group 1.4% (95% CI 0.27- 2.72%). There were more AEs categorized as intraocular pressure increased transient in the pooled brolucizumab 6 mg group: 1.4% (95% CI 0.27%-3.26%) vs. compared to the pooled aflibercept 2 mg group 0.5% (95% CI 0.00-1.66%).

Table 48: Other AESI in the loading phase (S-db 1)

		CRTH258B2301	Pooled	
		28 weeks	28 weeks	28 weeks
Category	Measurement	Bro 3mg N=190	Bro 6mg N=368	Afl 2mg N=368
Number of subjects with at least one AE	n (%) [E]	25 (13.2)[29]	47 (12.8)[58]	37 (10.1)[46]
Ocular Arterial Thromboembolic Events	n (%) (95% CI) [E]	1 (0.5)[1]	3 (0.8) (0.17,2.36)[3]	0 (0.0) (0.00,1.00)[0]
	RD Wk 28 (95% CI)		0.8 (-6.54, 8.16)	
Non-ocular Arterial Thromboembolic Events	n (%) (95% CI) [E]	2 (1.1)[2]	9 (2.4) (1.06,4.23)[9]	5 (1.4) (0.27,2.72)[5]
	RD Wk 28 (95% CI)		1.1 (-0.82,3.09)	
Hypertension	n (%) (95% CI) [E]	14 (7.4)[16]	26 (7.1) (4.19,10.85)[29]	27 (7.3) (4.81,10.43)[32]
	RD Wk 28 (95% CI)		-0.3 (-4.08,3.80)	
Intraocular pressure increased transient	n (%) (95% CI) [E]	2 (1.1)[2]	5 (1.4) (0.27,3.26)[8]	2 (0.5) (0.00,1.66)[2]
	RD Wk 28 (95% CI)		0.8 (-1.10,3.17)	
Non-ocular haemorrhage	n (%) (95% CI) [E]	7 (3.7)[8]	5 (1.4) (0.27,3.26)[7]	4 (1.1) (0.27,2.21)[6]
	RD Wk 28 (95% CI)		0.3 (-1.38,2.38)	
Retinal detachment and retinal tear	n (%) (95% CI) [E]	0 (0.0)[0]	1 (0.3) (0.01,1.50)[1]	1 (0.3) (0.01,1.50)[1]
	RD Wk 28 (95% CI)		0.0 (-7.35, 7.35)	
Venous thromboembolic events	n (%) (95% CI) [E]	0 (0.0)[0]	1 (0.3) (0.01,1.50)[1]	0 (0.0) (0.00,1.00)[0]
	RD Wk 28 (95% CI)		0.3 (-7.08, 7.62)	

CHMP assessment report
EMA/23630/2020 Page 99/125

Table 49: Forest plot for other AESI including incidences and risk differences for pooled brolucizumab 6 mg vs. pooled aflibercept 2 mg, by category (S-db 1)



- **52 weeks S-db**

The percentage of subjects with at least one event categorized under the other safety topics of interest of hypertension, non-ocular hemorrhage, retinal detachment and retinal tear and venous thromboembolic events were similar in the pooled brolucizumab 6 mg and pooled aflibercept 2 mg group in the 52 week safety database.

There was one additional event categorized as ocular arterial thromboembolic after Week 28 (Table 50) in the pooled brolucizumab 6 mg and pooled aflibercept 2 mg treatment groups.

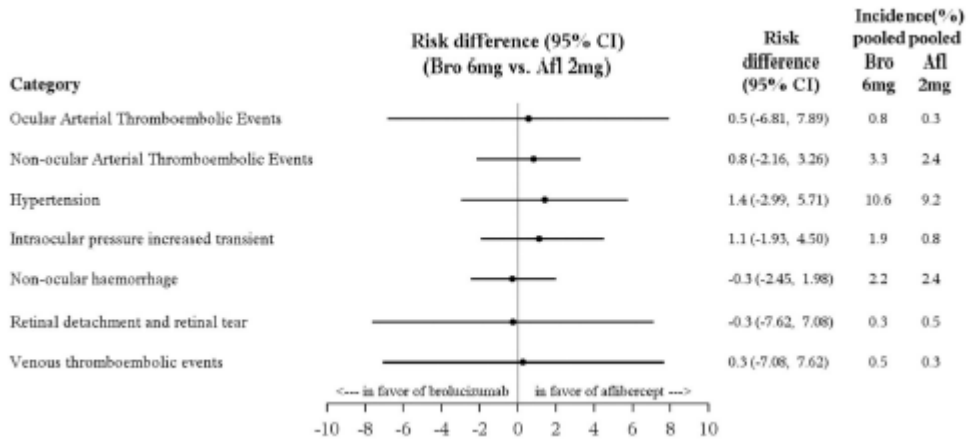
The subjects who had events categorized as ocular arterial thromboembolic events in the pooled brolucizumab 6 mg group was 0.8% vs. 0.3% in the pooled aflibercept 2 mg group in the 52 week safety database. Events categorized as non-ocular arterial thromboembolic events were reported in 3.3% of subjects in the pooled brolucizumab 6 mg group compared to the 2.4% in the pooled aflibercept 2 mg group. There were more AEs categorized as intraocular pressure increased transient in the pooled brolucizumab 6 mg group: 1.9% vs. 0.8% in the pooled aflibercept 2 mg group.

CHMP assessment report
EMA/23630/2020 Page 100/125

Table 50: Other AESI ion the maintenance phase (S-db 3)

		CRTH258B2301	Pooled	
Category	Measurement	Bro 3mg N=190	Bro 6mg N=368	Afl 2mg N=368
Number of subjects with at least one AE	n (%) [E]	37 (19.5)[47]	66 (17.9)[83]	52 (14.1)[77]
Ocular Arterial Thromboembolic Events	n (%) (95% CI) [E]	1 (0.5)[1]	3 (0.8) (0.17,2.36)[3]	1 (0.3) (0.01,1.50)[1]
	RD Wk 52 (95% CI)		0.5 (-6.81, 7.89)	
Non-ocular Arterial Thromboembolic Events	n (%) (95% CI) [E]	3 (1.6)[3]	12 (3.3) (1.59,5.16)[13]	9 (2.4) (0.83,4.81)[10]
	RD Wk 52 (95% CI)		0.8 (-2.16,3.26)	
Hypertension	n (%) (95% CI) [E]	19 (10.0)[24]	39 (10.6) (7.26,14.81)[44]	34 (9.2) (6.08,13.32)[47]
	RD Wk 52 (95% CI)		1.4 (-2.99,5.71)	
Intraocular pressure increased transient	n (%) (95% CI) [E]	5 (2.6)[6]	7 (1.9) (0.28,4.50)[10]	3 (0.8) (0.00,2.45)[3]
	RD Wk 52 (95% CI)		1.1 (-1.93,4.50)	
Non-ocular haemorrhage	n (%) (95% CI) [E]	8 (4.2)[10]	8 (2.2) (0.82,4.08)[10]	9 (2.4) (1.07,4.28)[12]
	RD Wk 52 (95% CI)		-0.3 (-2.45,1.98)	
Retinal detachment and retinal tear	n (%) (95% CI) [E]	1 (0.5)[1]	1 (0.3) (0.01,1.50)[1]	2 (0.5) (0.07,1.95)[3]
	RD Wk 52 (95% CI)		-0.3 (-7.62, 7.08)	
Venous thromboembolic events	n (%) (95% CI) [E]	2 (1.1)[2]	2 (0.5) (0.07,1.95)[2]	1 (0.3) (0.01,1.50)[1]
	RD Wk 52 (95% CI)		0.3 (-7.08, 7.62)	

Table 51: Forest plot for other AESI including incidences and risk differences for pooled brolucizumab 6 mg vs. pooled aflibercept 2 mg, by category (S-db 3)



For other AESI such as non-ocular AE, few differences were observed at week 52. Due to low number of cases reported, interpretation of differences is challenging.

CHMP assessment report
EMA/23630/2020 Page 101/125

Hypertension, non-ocular hemorrhage, non-ocular ATE and VTE are known risks of anti-VEGF by IV formulation used in oncology. In clinical trials and in post-marketing, cases are reported with IVT but considering confounding factors and low systemic exposure in case of IVT administration, causal relationship is not established. These topics are listed in the RMP as important potential risks and will be closely monitored in post-marketing setting.

Transient IOP increase is a common AE of all anti-VEGF by IVT route AND is related to IVT administration. A warning in the product information recommends monitoring and special precautions. IOP increase is also listed as important identified risk in the RMP and will be closely monitored in post-marketing setting.

Laboratory findings

Clinical chemistry

HbA1c

- **Loading S-db 1 and 2**

A box plot displaying the change from baseline for HbA1c for Loading pool 1 by treatment group (pooled brolucizumab 6 mg group and pooled aflibercept 2 mg group) and visit reported no differences between the treatment groups in terms of change from baseline in HbA1c.

- **52 weeks S-db**

A box plot displaying the change from baseline for HbA1c for 52 week safety database by treatment group (pooled brolucizumab 6 mg group and pooled aflibercept 2 mg group) and visit, until Week 52, reported no differences between the treatment groups in terms of change from baseline in HbA1c.

Study B2301 and B2302

Overall, in both individual studies, there were no meaningful differences between the treatment groups for subjects with clinically notable laboratory values at any visit. There were no differences between the treatment arms in terms of change from baseline for any of the laboratory parameters.

Vital signs, physical findings, and other observations related to safety

Blood pressure

- **Loading S-db 1 and 2**

No clinically relevant changes from Baseline to Week 28 were observed in any pooled treatment group of the Loading safety database 1 for mean change from baseline in systolic blood, diastolic blood pressure and pulse rate.

- **52 weeks S-db**

No clinically relevant changes from Baseline to Week 52 were observed in any pooled treatment group of the week 52 safety database for mean change from baseline in systolic blood pressure, diastolic blood pressure and pulse rate.

BVCA

The number and percentage of subjects with a loss in BCVA of ≥ 15 letters, ≥ 30 letters (study eye) from Baseline to each post-baseline visit, to the last visit and maximum loss at any visit were studied by treatment group for the Loading safety database 1 and the 52 week safety database. During the study

CHMP assessment report
EMA/23630/2020 Page 102/125

period loss in BCVA of ≥ 15 letters and/or ≥ 30 letters was similar between the pooled brolucizumab 6 mg group and pooled aflibercept 2 mg group.

- **Loading S-db 1 and 2**

There were no relevant differences between treatment groups (pooled brolucizumab 6 mg group and pooled aflibercept 2 mg group) of the Loading safety database 1 with respect to loss in BCVA of ≥ 15 letters and ≥ 30 letters at all visits. The number of subjects with loss in BCVA ≥ 15 letters and ≥ 30 letters was very low and similar between treatment groups of the Loading safety database at each visit. Note that loss in BCVA could be for any reason and not necessarily specifically related to being reported as an AE.

From Baseline to the maximum loss at any visit, the proportion of subjects with a loss in BCVA ≥ 15 letters and ≥ 30 letters was also similar across treatment groups of the Loading safety database 1 (Table 52).

Table 52: Loss in best corrected visual acuity (letters read): number (%) of subjects who lost BCVA in the study eye from baseline to the maximum loss at any visit (Loading S-db 1)

	CRTH258B2301	Pooled	
	28 weeks	28 weeks	28 weeks
Maximum loss in BCVA at any visit	Bro 3mg N=190 n/M (%)	Bro 6mg N=368 n/M (%)	Afl 2mg N=368 n/M (%)
≥ 15 letter loss	2/189 (1.1)	6/366 (1.6)	5/367 (1.4)
≥ 30 letter loss	1/189 (0.5)	1/366 (0.3)	1/367 (0.3)

- **52 weeks S-db**

There were no meaningful differences between treatment groups (pooled brolucizumab 6 mg group and pooled aflibercept 2 mg group) of the 52 week safety database with respect to loss in BCVA of ≥ 15 letters and ≥ 30 letters at any visit. The number of subjects with loss in BCVA ≥ 15 letters and ≥ 30 letters was very low and similar between treatment groups of the 52 week safety database each visit.

From Baseline to the maximum loss at any visit, the proportion of subjects with a loss in BCVA ≥ 15 letters and ≥ 30 letters was also similar across treatment groups of the 52 week safety database 1 (Table 53).

A small proportion of subjects (2 subjects in Study B2301 and 1 subject in Study B2302) who had a BCVA loss of ≥ 15 letters but < 30 letters at Week 52 compared to baseline were also reported to have had AESIs. One subject in the brolucizumab 6 mg group in Study B2302 with iridocyclitis and uveitis lost 16 letters compared to baseline at the early exit visit. One subject in the brolucizumab 3 mg group in Study B2301 with 2 events of iridocyclitis and 1 event of vitritis lost 22 letters from baseline at the Week 52 visit. One subject in the aflibercept 2 mg group in Study B2301 with an SAE of endophthalmitis lost 29 letters from baseline at the early exit visit.

There were 3 subjects (2 subject in Study B2301 and 1 subject in Study B2302) who were reported to have had AESIs and had a BCVA loss of ≥ 30 letters at Week 52 compared to baseline. One subject in the brolucizumab 6 mg group in Study B2302 with retinal vascular occlusion had lost 75 letters at the early exit visit. One subject in the brolucizumab 3 mg group in Study B2301 with endophthalmitis had lost 74 letters at the Week 52 visit. One subject in the brolucizumab 3 mg group in Study B2301 with 3 events of iridocyclitis and 1 event of retinal vein thrombosis lost 39 letters from baseline at the Week 52 visit.

CHMP assessment report
EMA/23630/2020 Page 103/125

Table 53: Loss in best corrected visual acuity (letters read): number (%) of subjects who lost BCVA in the study eye from baseline to the maximum loss at any visit (52 Week S-db)

	CRTH258B2301	Pooled	
Maximum loss in BCVA at any visit	Bro 3mg N=190 n/M (%)	Bro 6mg N=368 n/M (%)	Afl 2mg N=368 n/M (%)
≥ 15 letter loss	6/189 (3.2)	12/366 (3.3)	9/367 (2.5)
≥ 30 letter loss	4/189 (2.1)	1/366 (0.3)	3/367 (0.8)

IOP increase

IOP was measured in the study eye pre-injection and/or post-injection at every scheduled visit in both pivotal studies.

- **Loading S-db 1 and 2**

The proportion of subjects with observed pre-injection IOP ≥ 21mmHg at 3 consecutive scheduled visits in the Loading safety database 1 was similar in both treatment groups (10 subjects (2.7%) in the pooled 6 mg brolucizumab and 7 subjects (1.9%) in pooled aflibercept 2 mg group.

- **52 weeks S-db**

The proportion of subjects with observed pre-injection IOP ≥ 21mmHg at 3 consecutive scheduled visits in the 52 week safety database was the same in both treatment groups (10 subjects (2.7%) in the pooled 6 mg brolucizumab and 10 subjects (2.7%) in pooled aflibercept 2 mg group.

Safety in special populations

1- Intrinsic factors

- **Loading S-db 1 and 2**

Exposure to drug

There were no relevant differences between pooled brolucizumab 6 mg and pooled aflibercept 2 mg groups in exposure to study drug from Baseline to Week 28 across subgroups by age, gender, race, ethnicity, baseline BCVA and baseline HbA1c.

AE

There were no clinically relevant differences in the incidence of ocular AEs in the study eye and non-ocular AEs from Baseline to Week 28 across subgroups by age, gender, race, and ethnicity, baseline BCVA, and baseline HbA1c.

Serious AE

There were no clinically relevant differences between pooled brolucizumab 6 mg and pooled aflibercept 2 mg groups in the incidence of ocular SAEs in the study eye and non-ocular SAEs from Baseline to Week 28 across subgroups by age, gender, race, and ethnicity, baseline BCVA, and baseline HbA1c.

- **52 week S-db**

Exposure to drug

CHMP assessment report
EMA/23630/2020 Page 104/125

There were no clinically relevant differences between pooled brolucizumab 6 mg and pooled aflibercept 2 mg groups in the mean exposure to study drug at Week 52 across subgroups by age, gender, race, ethnicity, baseline BCVA and baseline HbA1c.

AE

There were no clinically relevant differences between pooled brolucizumab 6 mg and pooled aflibercept 2 mg groups in the incidence of ocular AEs in the study eye and non-ocular AEs from Baseline to Week 52 across subgroups by age, gender, race, and ethnicity, baseline BCVA, and baseline HbA1c.

Serious AE

There were no clinically relevant differences between pooled brolucizumab 6 mg and pooled aflibercept 2 mg groups in the incidence of ocular SAEs in the study eye and non-ocular SAEs from Baseline to Week 52 across subgroups by age, gender, race, and ethnicity, baseline BCVA, and baseline HbA1c.

Study B2301 - Subgroup analyses of safety data by Japanese ancestry

Safety data for the Japanese subgroup is summarized in Study B2301 and was generally comparable with that of the overall population and subjects of non-Japanese ethnicity.

2- Extrinsic factors

No subgroup analyses by extrinsic factors were performed.

Immunological events

In Studies B2301 and B2302, neither the pre-existing anti-drug antibodies (ADA) status nor the pre-existing nAb status of a subject had an impact on subsequent incidence of ocular AESIs.

Based on the result of immunogenicity assessment with brolucizumab from both Study B2301 and Study B2302, 18.3% of subjects with a boosted or induced ADA status had at least 1 AESI in the study eye, while 1.1% of subjects with a negative or positive ADA status with no boost had an AESI (

Table 54). Also, in Study B2301, 7/30 (23.3%) and 6/32 (18.8%) subjects with an integrated induced or boosted ADA status, in the brolucizumab 3 mg and 6 mg arms, respectively, experienced at least 1 AESI in the study eye. This compares with 3/148 (2.0%) and 1/143 (0.7%) subjects, respectively, with negative ADA status or positive ADA status with no boost. Similarly, in Study B2302, 2/20 (10.0%) subjects with an integrated induced or boosted ADA status had at least 1 AESI in the study eye, while 1/149 (0.7%) subjects with negative ADA status or positive ADA status with no boost had at least 1 AESI in the study eye. While the incidence of AESI was higher in subjects with treatment-emergent ADA, however, in this population, most of the subjects (67/82 (81.7%)) with treatment-induced or treatment-boosted ADA did not experience an AESI.

CHMP assessment report
EMA/23630/2020 Page 105/125

Table 54: ADA status up to Week 52 and incidence of AESI in the study eye

Study/Treatment N	ADA status up to Week 52	At least 1 AESI	No AESI	Total
Study B2301				
Brolucizumab 3 mg	ADA-negative or no boost	3 (2.0%)	145 (98.0%)	148 (100%)
(N = 190)	Induced or boosted	7 (23.3%)	23 (76.7%)	30 (100%)
	Total	10 (5.6%)	168 (94.4%)	178 (100%)
Brolucizumab 6 mg	ADA-negative or no boost	1 (0.7%)	142 (99.3%)	143 (100%)
(N = 189)	Induced or boosted	6 (18.8%)	26 (81.3%)	32 (100%)
	Total	7 (4.0%)	168 (96.0%)	175 (100%)
Study B2302				
Brolucizumab 6 mg	ADA-negative or no boost	1 (0.7%)	148 (99.3%)	149 (100%)
(N = 179)	Induced or boosted	2 (10.0%)	18 (90.0%)	20 (100%)
	Total	3 (1.8%)	166 (98.2%)	169 (100%)

- n = Number of subjects satisfying the condition.
- % are based on column totals within each treatment and category.
- AEs started after the subject discontinued study treatment and started alternative DME treatment in the study eye are censored

A similar trend was seen for simple ADA positivity as seen in Table 55; 4.4% of ADA positive subjects and 1.6% of ADA negative subjects had an AESI. In Study B2301, 9/145 (6.2%) and 6/138 (4.3%) ADA-positive (either pre-dose or post-dose) subjects treated with brolucizumab 3 mg and 6 mg, respectively, had at least 1 AESI compared with 1/40 (2.5%) and 1/43 (2.3%) ADA-negative subjects, respectively. In Study B2302, in the brolucizumab 6 mg arm, 3/129 (2.3%) ADA-positive subjects had at least 1 AESI in the study eye, while 0/42 ADAnegative subjects had an AESI in the study eye. The incidence of AESI was higher in subjects with positive ADA status, however, the vast majority (394/412 (95.6%)) of ADA positive subjects did not experience an AESI suggesting that the mere presence of ADA in and of itself is not sufficient to lead to an AESI.

CHMP assessment report
EMA/23630/2020 Page 106/125

Table 55: ADA positivity and the incidence of AESI

Study/Treatment N	ADA status	At least 1 AESI	No AESI	Total
Study B2301				
Brolucizumab 3 mg (N = 190)	Only ADA-negative status	1 (2.5%)	39 (97.5%)	40 (100%)
	At least 1 positive ADA status*	9 (6.2%)	136 (93.8%)	145 (100%)
	Total	10 (5.4%)	175 (94.6%)	185 (100%)
Brolucizumab 6 mg (N = 189)	Only ADA-negative status	1 (2.3%)	42 (97.7%)	43 (100%)
	At least 1 positive ADA status*	6 (4.3%)	132 (95.7%)	138 (100%)
	Total	7 (3.9%)	174 (96.1%)	181 (100%)
Study B2302				
Brolucizumab 6 mg (N = 179)	Only ADA-negative status	0 (0%)	42 (100%)	42 (100%)
	At least 1 positive ADA status*	3 (2.3%)	126 (97.7%)	129 (100%)
	Total	3 (1.8%)	168 (98.2%)	171 (100%)

Regarding the nAb status, while no association with AESI is observed in subjects with a pre-existing nAb positive status or in subjects with only negative nAb status, an association is observed between treatment-emergent nAb status and AESI as seen in Table 56.

In Study B2301, 8/40 (20.0%) subjects in the brolucizumab 3 mg arm and 6/46 (13%) subjects in the brolucizumab 6 mg arm with at least one positive post-dose nAb status, experienced at least 1 AESI in the study eye. This compares with the 13 subjects in the brolucizumab 3 mg arm and 12 subjects in the brolucizumab 6 mg arm with a pre-existing nAb positive status where 1/13 (7.7%) and 0/12 subjects, respectively, experienced at least 1 intraocular AESI in the study eye. Similarly, 1/131 (0.8%) subjects in the brolucizumab 3 mg arm and 1/122 (0.8%) subjects in the brolucizumab 6 mg arm, respectively, with only negative nAb status including those with a negative ADA status who by definition are considered nAb negative, experienced at least 1 AESI in the study eye.

In Study B2302, 3/43 (7.0%) subjects in the brolucizumab 6 mg arm with positive nAb status or a pre-existing nAb positive status, had at least 1 AESI in the study eye while no subjects out 6 with a pre-existing nAb positive status and no subjects out of 121 subjects in the brolucizumab 6 mg arm, with only negative nAb status (including those with a negative ADA who by definition are considered nAb negative) had an AESI in the study eye.

CHMP assessment report
EMA/23630/2020 Page 107/125

Table 56: Integrated nAb status and the incidence of AESI

Study/Treatment (No. of subjects)	nAb status up to Week 52	Incidence of AESI		
		At least 1 AESI	No AESI	Total
Study B2301				
Brolucizumab 3 mg	Only negative nAb status*	1 (0.8%)	130 (99.2%)	131 (100%)
(N=190)	At least one positive post-dose nAb status**	8 (20.0%)	32 (80.0%)	40 (100%)
	Pre-existing nAb positive	1 (7.7%)	12 (92.3%)	13 (100%)
	Total	10 (5.4%)	174 (94.6%)	184 (100%)
Brolucizumab 6 mg	Only negative nAb status*	1 (0.8%)	121 (99.2%)	122 (100%)
(N=189)	At least one positive post-dose nAb status**	6 (13.0%)	40 (87.0%)	46 (100%)
	Pre-existing nAb positive	0 (0%)	12 (100%)	12 (100%)
	Total	7 (3.9%)	173 (96.1%)	180 (100%)
Study B2302				
Brolucizumab 6 mg	Only negative nAb status*	0 (0%)	121 (100%)	121 (100%)
(N=179)	At least one positive post-dose nAb status**	3 (7.0%)	40 (93.0%)	43 (100%)
	Pre-existing nAb positive	0 (0%)	6 (100%)	6 (100%)
	Total	3 (1.8%)	167 (98.2%)	170 (100%)

However, as with treatment-emergent ADA, across both studies, while the incidence of AESI was higher in subjects with at least one positive post-dose nAb status, even in this population, the vast majority of subjects, 112/129 (86.8%), with at least one positive post-dose nAb positive status did not experience an AESI suggesting that the mere presence of nAb in and of themselves is not sufficient to lead to an AESI.

Alternatively, instead of looking specifically at treatment-emergent positive nAb status, an association can also be made with simple nAb positivity (integrated positive nAb status), combining the subjects with at least one positive post-dose nAb status and those with pre-existing nAb positive status. As seen in Table 56, in Study B2301 out of 53 subjects in the brolucizumab 3 mg arm and 58 subjects in the brolucizumab 6 mg arm with at least one positive post-dose nAb status or a pre-existing nAb positive status, 9/53 (17.0%) and 6/58 (10.3%) subjects, respectively, experienced at least 1 intraocular AESI in the study eye. Similarly, in Study B2302, out of 49 subjects in the brolucizumab 6 mg arm with at least one positive postdose nAb status or pre-existing nAb positive status, 3/49 (6.1%) subjects had at least 1 AESI in the study eye.

In conclusion:

- Pre-existing anti-brolucizumab antibodies, whether they were neutralizing or not, did not have an impact on subsequent incidence of AESIs.

- A higher incidence of AESI was observed in subjects with an integrated treatment-induced or treatment-boosted ADA status. A similar trend was seen for simple ADA positivity.

- A higher incidence of AESI was observed in subjects with at least one positive post-dose nAb status. A similar trend was seen for those with an integrated positive nAb status.

- While the incidence of AESI was higher in subjects with positive ADA (but only 4.4% of ADA positive subjects experienced an AESI), the vast majority (95.6%) of ADA positive subjects did not experience

CHMP assessment report
EMA/23630/2020 Page 108/125

an AESI. Similarly, most of the subjects with treatment-emergent ADA (81.7%) did not experience an AESI, suggesting that the mere presence of ADA, or treatment-induced or treatment-boosted ADA, in and of themselves is not sufficient to lead to an AESI. Furthermore, since the vast majority (95.6%) of ADA positive subjects did not experience an AESI, ADA positivity (including nAb positivity) alone cannot be used to predict which subjects might develop an AESI.

Safety related to drug-drug interactions and other interactions

No specific drug interaction studies were performed with brolucizumab.

Use in pregnancy and breastfeeding

Risk Summary

There are no adequate and well-controlled studies of brolucizumab administration in pregnant women. The potential risk of use of brolucizumab in pregnancy is unknown.

In all clinical studies included in this submission (Study B2301, Study B2302, Study B2304 and Study B2305) all women of childbearing potential (defined as women physiologically capable of becoming pregnant) were excluded from study participation unless they agreed to use highly effective methods of contraception.

Up to Week 52, one pregnancy was reported in Study B2301 (1 subject in the brolucizumab 6 mg arm); the subject discontinued study treatment as a result of the pregnancy. Follow-up information on this subject (post 52 week data cut-off) reported that the subject gave birth following emergency caesarian section. No birth defect was reported in the infant.

A study in pregnant cynomolgus monkeys did not indicate any harmful effects with respect to pre- or postnatal development at approximately 6-times the human systemic exposure based on serum Cmax (see Animal data).

Animal data

In an enhanced pre- and postnatal development (ePPND) study (TOX-R1670189-PPND) in pregnant cynomolgus monkeys, brolucizumab was administered to all animals by intravitreal (IVT) injection to one eye at doses of 3 or 6 mg once every 4 weeks until delivery. One additional injection was administered to a subset of animals 28 days post-partum and had blood and milk collected for toxicokinetic evaluations. There was no impact of IVT administration of brolucizumab on embryo-fetal development, pregnancy or parturition; or on the survival, growth, or postnatal development of offspring. This represents an exposure approximately 6- times the human exposure (based on serum Cmax) at the proposed clinical dose of 6 mg.

However, VEGF inhibition has been shown to affect follicular development, corpus luteum function, and fertility. Based on the mechanism of action of VEGF inhibitors, there is a potential risk to female reproduction and to embryo-fetal development.

Lactation

It is unknown if brolucizumab is transferred into human milk after administration of brolucizumab. There are no data on the effects of brolucizumab on the breastfed child or on milk production. In an ePPND study, brolucizumab was not detected in the maternal milk or infant serum of cynomolgus monkeys. Because of the potential for adverse drug reactions in the breastfed child, breastfeeding is not

CHMP assessment report
EMA/23630/2020 Page 109/125

recommended during treatment and for at least one month after the last dose when stopping treatment with brolucizumab.

Overdose

No new information about overdose has been generated in support of this application.

To date, there have been no reported cases of 'overdose' in humans related to the use of brolucizumab as brolucizumab must be administered by a qualified ophthalmologist.

Drug abuse

There is no known potential for abuse of brolucizumab considering that as advised in the current CDS, brolucizumab must be administered by a qualified ophthalmologist experienced in IVT injections.

Withdrawal and rebound

No studies have been conducted to assess withdrawal and rebound effects.

Effects on ability to drive or operate machinery or impairment of mental ability

Patients may experience temporary visual disturbances after an intravitreal injection with brolucizumab and the associated eye examination, and should therefore be advised not to drive or use machinery until visual function has recovered sufficiently.

Ocular AEs are described in detail above.

Impact of COVID-19 on safety results in Study B2301 and Study B2302

The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARSCoV- 2), was first identified by the WHO in Dec 2019. Due to the COVID-19 pandemic, changes to the conduct of Study B2301 and Study B2302 and planned analysis were implemented to ensure the safety and well-being of study participants, and to enable study oversight and compliance with the study protocol.

Study B2301

There was an impact of COVID-19 pandemic on the number of protocol deviations driven by under treatment. Nevertheless, in terms of results, no difference was observed between the treatment arms in exposed/non-exposed and impacted/non-impacted subgroups. A total of 2 subjects (both in the brolucizumab 3 mg arm) reported COVID-19 infection during the study. The analysis of safety data by COVID-19 exposed/non-exposed and impacted/non-impacted subgroups showed generally robust and comparable results with those observed for the overall population.

Study B2302

There was an impact of COVID-19 pandemic on the number of protocol deviations driven by under treatment in this study. Nevertheless, in terms of results, no difference was observed between the two treatment arms in exposed and non-exposed groups. A total of 2 subjects (1 in the brolucizumab 6 mg arm and one in the aflibercept 2 mg arm each treatment arm) reported COVID-19 infection during the study, which was fatal for the subject in the brolucizumab 6 mg arm. The analysis of safety data by COVID- 19 exposed and non-exposed subgroups showed generally robust and consistent results with the ones observed for the overall population.

Discontinuation due to adverse events

CHMP assessment report
EMA/23630/2020 Page 110/125

- **Loading S-db 1 and 2**

-Ocular AE

In the Loading safety databases 1 & 2, at Week 28, a total of 11 subjects in all treatment groups experienced at least 1 AE in the study eye that led to permanent study drug discontinuation: 4 subjects (1.1%) in the pooled brolucizumab 6 mg group, 3 subjects (0.8%) in the pooled aflibercept 2 mg group and 4 subjects (2.1%) in the brolucizumab 3 mg group in Study B2301 (Table 57).

The PT of the AEs which led to discontinuation of study treatment were reported only once in Loading safety database 1 (at Week 28) apart from uveitis: 2 subjects (0.5%) in the pooled brolucizumab 6 mg group, 1 subject (0.3%) in the pooled aflibercept 2 mg group and 0 subjects in the brolucizumab 3 mg group in Study B2301). In addition, endophthalmitis was reported as an AE leading to study treatment discontinuation in 2 subjects (0.5%) in the pooled aflibercept 2 mg group and 0 subjects in either of the brolucizumab groups (Table 57).

Table 57: Ocular adverse events leading to permanent discontinuation in loading S-db 1&2

	CRTH258B2301	Pooled		
	28 weeks	28 weeks	28 weeks	20 weeks
Preferred Term	Bro 3mg N=190 n (%)	Bro 6mg N=368 n (%)	Afl 2mg N=368 n (%)	Afl 2mg N=368 n (%)
Number of subjects with at least one AE	4 (2.1)	4 (1.1)	3 (0.8)	2 (0.5)
Uveitis	0	2 (0.5)	1 (0.3)	0
Retinal artery occlusion	1 (0.5)	1 (0.3)	0	0
Diabetic retinal oedema	0	1 (0.3)	0	0
Intraocular pressure increased	1 (0.5)	0	0	0
Iridocyclitis	1 (0.5)	0	0	0
Macular fibrosis	1 (0.5)	0	0	0
Retinal vasculitis	1 (0.5)	0	0	0
Endophthalmitis	0	0	2 (0.5)	2 (0.5)

-Non-ocular AE

In Loading safety database 1, a total of 9 subjects in all treatment groups, experienced at least 1 non-ocular AE that led to permanent study drug discontinuation: 2 subjects (0.5%) in the brolucizumab 6 mg group, 4 subjects (1.1%) in the aflibercept 2 mg group and 3 subjects (1.6%) in the brolucizumab 3 mg group in Study B2301 (Table 58). There was a single occurrence of each AE with a specific preferred term only which led the subject to permanently discontinue study treatment.

CHMP assessment report
EMA/23630/2020 Page 111/125

Table 58: Non-ocular adverse events leading to permanent discontinuation in loading S-db 1&2

	CRTH258B2301	Pooled	
	28 weeks	28 weeks	28 weeks
Preferred Term	Bro 3mg N=190 n (%)	Bro 6mg N=368 n (%)	Afl 2mg N=368 n (%)
Number of subjects with at least one AE	3 (1.6)	2 (0.5)	4 (1.1)
Cardiac failure	0	1 (0.3)	0
Subdural haematoma	0	1 (0.3)	0
Angina pectoris	1 (0.5)	0	0
Cerebral haemorrhage	1 (0.5)	0	0
Diabetic nephropathy	1 (0.5)	0	0
Myocardial infarction	1 (0.5)	0	0
Acute myocardial infarction	0	0	1 (0.3)
Adenocarcinoma	0	0	1 (0.3)
Chronic kidney disease	0	0	1 (0.3)
Renal failure	0	0	1 (0.3)
Waldenstrom's macroglobulinaemia	0	0	1 (0.3)

- **52 weeks S-db**

-Ocular AE

In the 52 week safety database a total of 17 subjects in all treatment groups, experienced at least 1 AE in the study eye that led to permanent study drug discontinuation: 6 subjects (1.6%) in the brolucizumab 6 mg group, 6 subjects (1.6%) in the aflibercept 2 mg group and 5 subjects (2.6%) in the brolucizumab 3 mg group in Study B2301 (Table 59). Uveitis was the most frequently reported ocular AE leading to permanent study drug discontinuation (4 subjects overall, 3 subjects (0.8%) in the brolucizumab 6 mg group and 1 subject (0.3%) in the aflibercept 2 mg group.

Table 59: Ocular adverse events leading to permanent discontinuation in 52-week S-db

	CRTH258B2301	Pooled	
Preferred Term	Bro 3mg N=190 n (%)	Bro 6mg N=368 n (%)	Afl 2mg N=368 n (%)
Number of subjects with at least one AE	5 (2.6)	6 (1.6)	6 (1.6)
Uveitis	0	3 (0.8)	1 (0.3)
Retinal artery occlusion	1 (0.5)	1 (0.3)	1 (0.3)
Diabetic retinal oedema	0	1 (0.3)	0
Eye inflammation	0	1 (0.3)	0
Intraocular pressure increased	1 (0.5)	0	0
Iridocyclitis	1 (0.5)	0	0
Macular fibrosis	1 (0.5)	0	0
Retinal detachment	1 (0.5)	0	0
Retinal vasculitis	1 (0.5)	0	0
Endophthalmitis	0	0	2 (0.5)
Iritis	0	0	1 (0.3)
Retinal aneurysm	0	0	1 (0.3)

-Non-ocular AE

In the 52 week safety database, a total of 20 subjects in all treatment groups, experienced at least 1 non-ocular AE that led to permanent study drug discontinuation. A similar proportion discontinued to at least 1 non-ocular AE in all 3 treatment groups: 8 subjects (2.2%) in the brolucizumab 6 mg group, 9 subjects (2.4%) in the aflibercept 2 mg group and 3 subjects (1.6%) in the brolucizumab 3 mg group in

CHMP assessment report
EMA/23630/2020 Page 112/125

Study B2301 (Table 60). There was a single occurrence of each AE with a specific preferred term only which led the subject to permanently discontinue study treatment.

Table 60: Non-ocular adverse events leading to permanent discontinuation in 52-week S-db

	CRTH258B2301	Pooled	
Preferred Term	Bro 3mg N=190 n (%)	Bro 6mg N=368 n (%)	Afl 2mg N=368 n (%)
Number of subjects with at least one AE	3 (1.6)	8 (2.2)	9 (2.4)
Anaphylactic reaction	0	1 (0.3)	0
Bickerstaff's encephalitis	0	1 (0.3)	0
COVID-19	0	1 (0.3)	0
Cardiac failure	0	1 (0.3)	0
Cerebellar stroke	0	1 (0.3)	0
Colon cancer	0	1 (0.3)	0
Diabetes mellitus inadequate control	0	1 (0.3)	0
Pancreatic carcinoma	0	1 (0.3)	0
Subdural haematoma	0	1 (0.3)	0
Angina pectoris	1 (0.5)	0	0
Cerebral haemorrhage	1 (0.5)	0	0
Diabetic nephropathy	1 (0.5)	0	0
Myocardial infarction	1 (0.5)	0	0
Acute myocardial infarction	0	0	1 (0.3)
Adenocarcinoma	0	0	1 (0.3)
Bronchial carcinoma	0	0	1 (0.3)
Cerebellar haemorrhage	0	0	1 (0.3)
Chronic kidney disease	0	0	1 (0.3)
Confusional state	0	0	1 (0.3)
Coronary artery disease	0	0	1 (0.3)
Ischaemic stroke	0	0	1 (0.3)
Renal failure	0	0	1 (0.3)
Waldenstrom's macroglobulinaemia	0	0	1 (0.3)

Post marketing experience

Brolucizumab has been marketed as Beovu® since the IBD of 07-Oct-2019 with the nAMD indication. Total post-marketing patient exposure based on the Beovu units (vials/PFS) sold worldwide since the IBD of the product is estimated to be approximately 31,000 patient-treatment years (PTY).

Post-marketing data for brolucizumab in the treatment of nAMD is being submitted on a regular basis as PSURs (since IBD of brolucizumab; 07-Oct-2019).

Literature searches of safety findings with brolucizumab treatment, are performed and reviewed on an ongoing basis in each PSUR from the date of the first authorization of the treatment of patients with nAMD (in the US) on 07-Oct-2019 (IBD); the most recent PSUR is [PSUR 07-Apr-2020 to 06-Oct-2020]. No new safety findings related to brolucizumab were retrieved from published peer-reviewed scientific literature or made available as unpublished manuscripts during the reporting interval.

Following reports of post-marketing AEs of 'Retinal vasculitis and/or retinal vascular occlusion' with brolucizumab, Novartis confirmed an emerging safety issue during the reporting period of the PSUR (07-Oct-2019 to 06-Apr-2020) on 06-Apr-2020; and the following actions were taken during the reporting period for the most recent PSUR [PSUR 07-Apr-2020 to 06-Oct-2020]:

A safety label change was submitted from 30-Apr-2020 onward and is included in the PSUR (reporting period of PSUR 07-Apr-2020 to 06-Oct-2020). The CDS was updated with the new safety issue 'Retinal vasculitis and/or retinal vascular occlusion' under 'Warnings and precautions' and 'Adverse drug reaction' sections. Additionally, this new safety topic was included as an important identified risk in the RMP

CHMP assessment report
EMA/23630/2020 Page 113/125

(version 3.1) during the reporting period of PSUR 07-Apr-2020 to 06-Oct-2020. Novartis performed an evaluation of cumulative data of retinal vasculitis and/or retinal vascular occlusion in the PSUR (PSUR 07-Apr-2020 to 06-Oct- 2020) and did not find any new information or a change in the severity of this identified risk.

The important identified risk 'Retinal vasculitis and/or retinal vascular occlusion' will continue to be further monitored and characterized in subsequent PSURs.

Apart from the new safety topic, leading to the safety label change described above a review of all data received during the PSUR interval reporting period in PSUR 07-Apr-2020 to 06-Oct-2020 did not reveal any new or changing safety information for brolucizumab and is consistent with the information present in the current labeling documents.

Taking all of the above into consideration, the benefit-risk assessment of brolucizumab remains positive in the approved indication of nAMD.

2.5.1. Discussion on clinical safety

The clinical safety analysis is based on two phase III studies (KESTREL and KITE) which assessed intravitreal administration of brolucizumab 6mg in patients with visual impairment due to diabetic macular oedema for 52 weeks. The randomized controlled study design allows for a comparison with intravitreal administration of aflibercept 2mg. Dosage of 3mg of brolucizumab was evaluated in only one study (KESTREL), thus comparison with other arms in more appropriate in KESTREL study than in pooled data.

Patient exposure

The two studies enrolled 926 patients including 368 who received brolucizumab 6mg, 368 who received aflibercept 2mg and 190 patients who received brolucizumab 3mg in KESTREL study.

Due to similar design, data were pooled into three databases: two for the loading phase (Sd-b 1 and 2) and one for the maintenance phase (Sd-b 3). Two databases were used for the loading phase since interval between doses are different for brolucizumab and aflibercept (6 and 4 weeks respectively). In the first one Sd-b 1, duration of treatment was similar for both arms (28 weeks) with different schedules of injections (most patients received 5 injections for brolucizumab and 6 for aflibercept) and in the second one Sd-b 2, duration of treatment was shorter for aflibercept (20 weeks) but with similar schedules of injections (most patients received 5 injections).

The majority of patients (>81%) completed the studies at week 52 with similar rates between groups. A slight higher number of injections was reported in aflibercept group (8.5 vs 6.9 in brolucizumab 6mg and 6.8 in brolucizumab 3mg) and could be explained by the different schedules of treatment during the loading phase but also during the maintenance phase (possibility of 12 weeks in brolucizumab group vs 8 weeks which was not allowed by protocol in aflibercept group).

The most reported reasons for discontinuation were subject decision (4.6% for brolucizumab 6mg, 4.2% for brolucizumab 3mg and 2.2% for aflibercept) and discontinuation due to adverse event (1.6% for brolucizumab 6mg, 2.6% for brolucizumab 3mg and 2.2% for aflibercept).

Patient demographics and baseline characteristics were consistent across treatment groups and reflect the DME population with a population younger than in AMD population (mean age of 63 years old with an overall range of 23 to 87). Slightly more men were included (≈64%), white population was more represented (>77%) as well as not Hispanic and Latino ethnicity (>70%).

CHMP assessment report
EMA/23630/2020 Page 114/125

Adverse event (AE)

Ocular AE

Incidence of ocular AE was similar in both periods between groups (in the loading phase: 24.2% in brolucizumab 6 mg vs 25% in aflibercept at week 28 and 21.2% at week 20 and in the maintenance phase: 35.1% in brolucizumab 6mg vs 34.0% in aflibercept). The most commonly reported AE was conjunctival haemorrhage in both periods with similar rates between arms (in the loading phase: 4.6% in brolucizumab 6 mg vs 5.7% in aflibercept at week 28 and 4.9% at week 20 and in the maintenance phase: 5.7% in brolucizumab 6mg vs 6.5% in aflibercept). Higher rates reported in pooled data for brolucizumab 3mg compared to other arms due to study effect were not reported in KESTREL study. Other frequently reported AE were vitreous floaters, eye pain, vitreous detachment and vision blurred, all listed ADR with no significant differences between groups.

AE of IOP increased, uveitis and iridocyclitis, the most frequently drug-related AE and related to IVT are also listed in the product information. Other known injection-related risks were retrieved such as retinal detachment.

Regarding intraocular inflammations, as for AMD indication, more AE were reported in brolucizumab groups in both periods (at week 52, risk difference of 1.6% (95% CI -0.83%;4.76%)). Most cases were reported early after treatment initiation and severity was mostly mild to moderate.

In both periods, similar proportions of serious ocular AE were reported between groups (in the loading phase: 1.1% in brolucizumab 6mg vs 0.8% in aflibercept at week 28 and 0.5% at week 20 and in the maintenance phase: 1.6% in brolucizumab 6mg vs 1.9% in aflibercept). Most reported serious AE were retinal vasculitis and endophthalmitis.

For endophthalmitis, which is associated with intravitreal administration, similar rates were reported between groups at week 52 and no safety issue emerged. Warnings are mentioned in the product information and patient educational materials are available to ensure that patients are adequately informed about signs and symptoms of this sight-threatening AE. Preferential use of the pre-filled syringe would allow to reduce this risk.

Cases of retinal vasculitis and retinal vascular occlusion, other sight-threatening eye conditions which emerged from US post-marketing setting in February 2020, were reported (retinal vasculitis: 1 case in brolucizumab 6mg, 2 in brolucizumab 3mg vs 0 in aflibercept group; retinal vascular occlusion: 2 cases in brolucizumab 6mg, 2 in brolucizumab 3mg vs 1 in aflibercept group). In one case in brolucizumab arm, significant vision loss was associated. Warnings have been implemented since launch through variation II/02 to alert about signs and symptoms of these AE. Risk factors associated retrieved from US retrospective real-world studies were also implemented through variation II/08 such as patients with medical history of intraocular inflammation/retinal vascular occlusion in the year prior the treatment with Beovu, as well as an immune cause identified based on a mechanistic study. Immune cause retrieved is consistent with immunologic data reported in KITE and KESTREL studies. Finally, other product information changes were implemented through variation II/06 based on 52-week first interpretable results of study MERLIN which revealed an increased incidence of IOI and related adverse events including RV and RVO in patients with every 4 weeks dosing beyond the "loading phase" in nAMD. A DHPC was thereafter sent in November 2021 to alert about these new information.

A potential higher risk in DME population of ocular arterial thromboembolic events including retinal artery occlusion compared to AMD patients was questioned due to almost comparable rates of RAO reported (0.7% vs 0.6%) but with lower duration of studies for DME (52 weeks vs 96 weeks) and few cases reported which made challenging comparison of data. However, considering an immunologic cause

CHMP assessment report
EMA/23630/2020 Page 115/125

retrieved for this event, a higher risk in DME patients may not be expected at this stage. This concern will be further investigated in post-marketing setting through PSUSA procedure.

Non-ocular AE

Incidence of non-ocular AE was similar in both periods between groups (in the loading phase: 49.5% in brolucizumab 6mg vs 51.1% in aflibercept and in the maintenance phase: 64.1% in brolucizumab 6mg, 67.7% in aflibercept). Higher rates reported in pooled data for brolucizumab 3mg compared to other arms due to study effect were not reported in KESTREL study.

As for AMD indication, the most reported SOC was Infections and infestations with nasopharyngitis as the most reported AE, a common AE in elderly population and unrelated to brolucizumab, with consistent rates across treatment groups. Hypertension was also frequently reported and similarly in both groups.

Regarding serious non-ocular AE, similar proportions were reported between groups in both periods (in the loading phase: 10.3% in brolucizumab 6mg vs 12.5% in aflibercept and in the maintenance phase: 17.7% in brolucizumab 6mg vs 20.1% in aflibercept).

Due to VEGF inhibition effect on microvasculature, hypertension as well as non-ocular haemorrhage and arterial and venous thromboembolic AE were particularly discussed as AESI. In most cases, patients had cardiovascular risk factors and none of them was assessed as related to the study drug. Considering low systemic exposure in case of IVT administration, causal relationship is not established. These AE are listed in the RMP as important potential risks and are closely monitored.

Immunogenicity

As previously observed in AMD indication, a correlation between ADA status and occurrence of intraocular inflammation was retrieved since a higher incidence of ocular AESI was observed in patients with positive ADA and positive nAb status. No impact of pre-existing antibodies (neutralizing or not) was retrieved. However, ADA status cannot be used to predict any ocular AESI occurrence including retinal vasculitis and retinal vascular occlusion since most patients with positive ADA -induced or boosted- or positive nAb status did not experience any ocular AESI. Additional investigations will be performed through ongoing clinical trials.

2.5.2. Conclusions on clinical safety

Overall, as for AMD indication, the safety profile of brolucizumab seems similar to aflibercept, already marketed, except for intraocular inflammations which are more reported with brolucizumab.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.5.4. Direct Healthcare Professional Communication

A DHPC was sent in November 2021 in the context of variation II/06 to alert health professionals about new information available related to IOI including retinal vasculitis and retinal vascular occlusion (immune cause retrieved, risk factors and increased risk with treatment interval less than 8 weeks in the maintenance phase).

CHMP assessment report
EMA/23630/2020 Page 116/125

2.5.5. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Beovu (brolucizumab) is included and remain in the additional monitoring list as a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Risk management plan

In the initial submission, the MAH submitted version 4.0 to address changed related to the new indication. In the second round of assessment, the MAH submitted an updated RMP v8.0, that is the consolidated version of RMP v7.0 approved through variation EMEA/H/C/0004913/II/0008 and incorporating also the changes made for the addition of DME as an indication originally in RMP v4.0.

Summary of significant changes in this RMP: Key changes made compared to RMP v3.0 are:

- Product information section is updated with proposed changes in the SmPC for the DME indication.
- Safety data from Study RTH258B2301 (KESTREL) and Study RTH258B2302 (KITE) has been added to support the new indication of visual impairment due to DME.
- Clinical trial exposure data and risk characterization data have been updated.
- Updates are made to targeted follow-up checklists for the important identified risk "Intraocular inflammation" and "Retinal vasculitis and/or retinal vascular occlusion"
- Information about patient educational material has been updated to cover the DME indication.

Part Major changes compared to RMP v 3.0

- **Part I**

Part I "Product overview" has been updated to include the new targeted indications and dosage in EEA. Information about current dosage is updated in line with SmPC.

- **Part II**

-Module SI has been revised to include epidemiology of the indication and target population

-Module SII has been revised to include key safety findings from non-clinical studies based on recently available non-clinical data

CHMP assessment report
EMA/23630/2020 Page 117/125

Table 3-1 → Key safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
Toxicity: • Key issues identified from acute or repeat dose toxicity studies No safety findings have been observed in any nonclinical study. Three- and six-month Good Laboratory Practice (GLP) studies were conducted in cynomolgus monkeys, with intravitreal injections of brolucizumab administered up to 6 mg/eye every 3 to 4 weeks. Evaluations included daily observations for morbidity and mortality, clinical observations (including abnormal respiration and behavior), body weight determinations, biomicroscopic and indirect ophthalmoscopic examinations, intraocular pressure (IOP) measurements, electroretinogram analysis, clinical pathology, toxicokinetic analysis of the serum and vitreous, anti-drug antibody (ADA) analysis of the serum and vitreous, and macroscopic and microscopic tissue examinations. No ocular or systemic toxicity /effects were noted in any study. Pre-existing ADA were measured before dosing on Day 1 and although there appeared to be an increase in ADA incidence and titer over time, there was no dose-response relationship and no correlation between ADA titers and systemic exposure or adverse effects in any study.	No ocular or systemic toxicities were noted in non-clinical studies conducted using the clinical dose and clinical route of exposure.
• A study in pregnant cynomolgus monkeys did not indicate any harmful effects with respect to pre- or postnatal development at approximately 6 times the human exposure based on serum Cmax. • In an enhanced pre- and postnatal development (ePPND) study, brolucizumab was not detected in the maternal milk or infant serum of cynomolgus monkeys.	There are no adequate and well-controlled studies of brolucizumab treatment in pregnant women. Based on the mechanism of action of VEGF inhibitors, there is a potential risk to female reproduction and to embryo-fetal development.

-Module SIII has been revised to include clinical trial exposure from study KITE and KESTREL

-Module SIV has been revised to include key exclusion criteria of pivotal DME studies

-Module SV has been revised to update post-authorization exposure data based on current PSUR

-Module SVII has been revised to update presentation of important identified and potential risks based on DME pivotal studies.

CHMP assessment report
EMA/23630/2020 Page 118/125

Part II Safety specification SVIII.1: Summary of safety concerns

Table Summary of safety concerns

Important identified risks	Intraocular inflammation
	Retinal vasculitis and/or retinal vascular occlusion
	Endophthalmitis
	Transient intraocular pressure increased
	Retinal detachment/ tear
Important potential risks	Non-ocular events (ATE, VTE, non-ocular haemorrhage, and hypertension)
Missing information	Safety beyond two years of treatment
	Non-ocular safety after bilateral treatment

- **Part III to V**

No changes have been made

In Part V regarding the educational material, the MAH accepted to add a separate chapter describing intraocular inflammation including retinal vasculitis and/or retinal vascular occlusion and identified risk factors as described in section 4.4 of the SmPC.

- **Part VI:** Summary of the risk management plan has been updated to reflect the corresponding changes made to Parts I and II of the RMP.

The Summary of the risk management plan has been updated accordingly.

- **Part VII** No changes were made to Annex 1 to Annex 3

Annex 4: Updates are made to targeted follow-up checklists for the important identified risk "Intraocular inflammation" and "Retinal vasculitis and/or retinal vascular occlusion"

No changes were made to Annex 5

Annex 6: Patient guide description have been updated to include the DME indication and editorial changes.

Annex 7 has been updated with brief statistical description and outputs, newly included internal references and literature citations.

Annex 8 was updated accordingly to reflect changes from previous version of RMP.

The Annexes have been updated accordingly besides Annex 6.

3.1. Overall conclusion on the RMP

RMP version 8.1 (DME) is acceptable.

CHMP assessment report
EMA/23630/2020 Page 119/125

4. Benefit-Risk Balance

4.1. Therapeutic Context

4.1.1. Disease or condition

Diabetic macular edema (DME) is characterised by exudative fluid accumulation in the macula. When the area of swelling involves the center of the macula, the fovea, it leads to clinical impairment of vision.

DME is a frequent manifestation of diabetic retinopathy (DR) and is the major cause of vision loss in patients with DR. Patients can develop DME at any stage during the progression of DR.

The pathophysiological processes begin with chronic hyperglycaemia, and interplay between vascular endothelial growth factor (VEGF) and inflammatory mediators.

Estimates of the prevalence of DME in patients with Type I and Type II DM range between 4.2% and 7.9%, and 1.4% and 12.8%, respectively (Lee et al 2015).

4.1.2. Available therapies and unmet medical need

The current treatment options for patients with visual impairment secondary to DME are: intravitreal anti-VEGF (which includes ranibizumab (Lucentis®), aflibercept (Eylea®)), laser photocoagulation, intravitreal corticosteroids, or intravitreal corticosteroid implants.

However, intravitreal anti-VEGF treatments can be a significant burden to patients. Thus, there is a need to develop therapies with a longer effect. Additionally, in the context where the efficacy of an anti-VEGF can reduce over the time and requires a switch to another anti-VEGF together with the fact some patients have a poor treatment effect to available therapies lead a need of additional alternatives therapies.

4.1.3. Main clinical studies

The clinical study program for the sought indication consists of 2 randomized, double-masked, multicenter, active-control (versus aflibercept 2 mg) studies, RTH258-B2301 (KESTREL study) and RTH258-B2302 (KITE study) to evaluate the safety and efficacy of brolucizumab administrated intravitreally. The total studies duration was 100 weeks. The main difference in study design were that B2301 study included a brolucizumab 3 mg treatment arm in addition to the 6 mg arm, while the 6 mg dose only has been investigated in B2302 study.

Patients in brolucizumab arms (3 mg and 6 mg) received 5 loading doses every 6 weeks (q6w) (Day 0, Week 6, Week 12, Week 18 and Week 24), followed by maintenance regimens every 12 weeks (q12w) or every 8 weeks (q8w) depending on the disease activity status. But patients in aflibercept arms received monthly 5 loading doses (Day 0, Week 4, Week 8, Week 12 and Week 16), followed by maintenance regimen every 8 weeks (q8w), and were not allowed to switch on a q12w regimen.

4.2. Favourable effects

In both pivotal Phase III studies, brolucizumab 6 mg demonstrated non-inferiority to aflibercept 2 mg in the treatment of the neovascular AMD. The primary endpoint was met in FAS as well in PPS analysis with consistent outcomes.

In B2301 study, regarding FAS population, the mean change in BCVA from Baseline at Week 52, with 95% CI, for Brolucizumab 6 mg and Aflibercept were respectively 9.2 [8.1, 10.3] and 10.5 [9.4, 11.7]

CHMP assessment report
EMA/23630/2020 Page 120/125

letters. In pairwise ANOVA, the non-inferiority of Brolucizumab 6 mg compared to Aflibercept were demonstrated with a LS mean difference -1.3 letters (95% C.I.: -2.9, 0.3; p<0.001).

In B2302 study, regarding FAS population, the mean change in BCVA from Baseline at Week 52, with 95% CI, Brolucizumab 6 mg and Aflibercept were respectively 10.6 [9.3, 11.9] and 9.4 [8.1, 10.7] letters. In pairwise ANOVA, the non-inferiority of Brolucizumab 6 mg compared to Aflibercept were demonstrated with a LS mean difference 1.2 letters (95% C.I.: -0.6, 3.1; p<0.001).

Primary outcomes were supported by the first key secondary endpoint, average change in BCVA from Baseline over the period Week 40 through Week 52.

Analysis of the other secondary endpoints related to anatomical parameters, in particular change from baseline in CSFT over the period Week 40 through Week 52 and presence of SRF and/or IRF at Week 52, provided supportive outcomes, giving reassurance on the efficacy of brolucizumab. Likewise, Quality of Life analysis were also supportive.

Regarding the assessment of the q12w regimen, second key secondary endpoint estimated that the probability, with 95% CI, for a subject on brolucizumab 6 mg to be maintained on the q12w regimen up to the disease activity assessment at Week 52 was 55.1% [46.9, 62.5] in B2301 study and 50.3 % [42.5, 57.7] in B2302 study.

Finally, analysis of the proportion of subjects with ≥2-step improvement in DRSS at Week 52 shown a non-inferiority of brolucizumab 6mg versus aflibercept with an estimated difference of 4.0% (95% CI: -0.6, 8.6; p<0.001). The proportion estimates, with 95% CI, were 28.9% [24.6, 34.3] in the brolucizumab 6 mg arm and 24.9% in the aflibercept 2 mg arm [20.3, 29.4]

4.3. Uncertainties and limitations about favourable effects

Absence of data makes difficult the generalization of the results in non-naïve-treatments subpopulation. Additionally, given that patients with active PDR are excluded of the study, the proportion of patients with a PDR was very limited making difficult the generalisation of the results in this subset.

The Applicant additional results showing that the HbA1c level seems stable in the brolucizumab and aflibercept groups over the study duration, reassuring adequate controlled diabetes. The downside is that there is no data in patients with poorly controlled diabetes (also in safety).

The non-inferiority margin of 4 is considered too broad and therefore not acceptable. However, this is overruled by the actual findings, as the lower limit of the confidence interval is within the 3 letter non-inferiority margin that has been accepted.

The multiple testing procedure for the pooled non-inferiority analysis of the DRSS endpoint based on both studies DR2301 and DR2302 is questionable. Nevertheless, the pooled analysis is deemed acceptable but requires a careful interpretation of the results, based on both achieved significance levels and their clinical relevance. Additionally, a further discussion on the adequacy of the control of the diabetes in patients enrolled in the studies, and its potential impact on the DRSS results is awaited. Finally, a sustained effect over time has to be shown; 24-Month data for DRSS analysis are thus needed.

4.4. Unfavourable effects

The safety profile of brolucizumab 6 mg in DME patients seems overall similar to the one described in the initial application for AMD population.

CHMP assessment report
EMA/23630/2020 Page 121/125

Dosage of 3mg was studied in KESTREK trial and no significant difference was reported compared to dosage of 6mg in terms of ocular, non-ocular AE and SAE.

Most common AE reported with brolucizumab 6mg pertained to SOC Eye disorders and the most reported AE was conjunctival haemorrhage (4.6% in the loading phase and 5.7% at 52 weeks). Similar rates were reported in aflibercept group.

Other AE related to injection procedure were reported at week 52 such as endophthalmitis (0.3%), IOP increased (1.9%), retinal pigment epithelial tears and retinal detachment (0.3%) and cataract (3.5%) with no difference compared to aflibercept group.

As for AMD indication, intraocular inflammation was more reported in brolucizumab group compared to aflibercept (2.7% vs 0.8%). Most of these events were mild and moderate and were observed early after treatment initiation. Most frequently PT terms retrieved were uveitis, iridocyclitis, retinal vasculitis, iritis and eye inflammation.

Four cases of retinal vascular occlusion which is an ophthalmological emergency were also reported with brolucizumab in the study eyes including one case with a significant vision loss versus 1 case in aflibercept arm. These AE are not listed in the product information of other anti-VEGF by IVT route. They have been identified and listed in the context of initial application in AMD indication. But few months after, in February 2020, an increase of incidence and severity emerged from US post-marketing setting and additional warnings were thus implemented into the product information. These AE were also listed in the RMP as important identified risks and further investigations were pursued. Risk factors were thereafter identified from US retrospective real world studies and a higher risk in patients with every 4 weeks dosing beyond the "loading phase" in nAMD based on MERLIN study was retrieved.

In the context of initial application, a correlation was made between intraocular inflammation and ADA status since a higher incidence was observed in patients with positive ADA status. Converging data were reported in DME studies between ADA status and ocular AESI including intraocular inflammation, retinal vasculitis and retinal vascular occlusion. However, since most patients with positive ADA or positive nAb status did not experience any ocular AESI, immunologic tests cannot be used to predict their occurrence.

Based on a mechanistic study, an immunologic cause of intraocular inflammation including retinal vasculitis and retinal vascular occlusion was identified in August 2021 by the Applicant. This topic will be further monitored in PSUR and in ongoing clinical trials

4.5. Uncertainties and limitations about unfavourable effects

Systemic safety profile is still unknown especially ATE, VTE, hypertension and non-ocular haemorrhage which are known AE of anti-VEGF by IV route. No major difference was observed between brolucizumab and aflibercept groups in DME studies despite low reporting rates which do make the comparison difficult to assess. Considering low systemic exposure, a relationship has not been established. These AE are listed in the RMP as important potential risks and will be closely monitored.

4.6. Effects Table

Table 1. Effects Table for brolucizumab 6 mg in the treatment of adult patients with visual impairment due to diabetic macular edema (Studies B2301 and B2302)

CHMP assessment report
EMA/23630/2020 Page 122/125

Effect	Short description	Unit	Brolucizumab 6mg	Aflibercept 2mg	Uncertainties / Strength of evidence	References
Favourable Effects						
Change from baseline in BCVA at Week 52	Primary endpoint (95% CI)	Letters (EDTRS)	9.2 (8.1, 10.3)	10.5 (9.4, 11.7)	- Consistent with PPS analysis - Supported by other secondary endpoints (BCVA and anatomical parameters) But: - Need of long term data, in particular to support q12w regimen - generalization of the results in the type I diabetes subpopulation and in non-naïve-treatments subpopulation need further discussion	B2301 study
			10.6 (9.3, 11.9)	9.4 (8.1, 10.7)		B2302 study
Average change in BCVA from Baseline over the period Week 40 through Week 52	First key secondary endpoint (95% CI)	Letters (EDTRS)	9.0 (7.9, 10.0)	10.5 (9.4, 11.5)		B2301 study
			10.3 (9.1, 11.5)	9.4 (8.2, 10.6)		B2302 study
Unfavourable Effects						
Conjunctival haemorrhage	Incidence	%	5.7	6.5	Most reported AE	(1)
Endophtalmitis, IOP increased, and retinal detachment and retinal tear	Incidence	%	0.3 1.9 0.3	0.5 0.8 0.5	AE related to injection procedure	(1)
Intraocular inflammation	Incidence	%	2.7	1.1	AE reported with a higher incidence compared to aflibercept	(1)
Retinal vasculitis	Incidence	%	0.3	0.0	Sight-treathening AE associated with brolucizumab and not listed with other anti-VEGF drugs by IVT route	(1)
Retinal vascular occlusion	Incidence	%	0.5	0.3	Sight-treathening AE associated with brolucizumab and not listed with other anti-VEGF drugs by IVT route	(1)
ATE VTE Hypertension Non-ocular haemorrhage	Incidence	%	3.2 0.5 10.6 2.2	2.4 0.3 9.2 2.4	Potential AE listed with anti-VEGF by IV route Not confirmed due to low systemic exposure	(1)

CHMP assessment report
EMA/23630/2020 Page 123/125

(1) Pooled safety data at 52 weeks

4.7. Benefit-risk assessment and discussion

4.7.1. Importance of favourable and unfavourable effects

Brolucizumab 6 mg demonstrated a similar benefit profile with the comparator, aflibercept. The non-inferiority was largely met in the primary and the first key secondary endpoint at Week 52. Moreover, analysis in FAS population and PPS population were consistent. Additionally, endpoints related to anatomical parameters and Quality of Life were supportive of the demonstration of the benefice.

Ocular safety profile of brolucizumab 6mg in DME patients appears to be similar to the one identified in AMD population. The most commonly reported AE was conjunctival haemorrhage with similar rates between aflibercept and brolucizumab arms.

Other AE known to be induced by anti-VEGF agents by IVT route and related to injection procedure were also reported with similar rates between both groups such as endophthalmitis, IOP increase, cataract, and retinal tear/detachment.

As for AMD indication, incidence of intraocular inflammation including retinal vasculitis was higher than in aflibercept group. Retinal vascular occlusions cases were also more reported in brolucizumab arms. Warnings have been implemented in the product information and an immunologic cause has been retrieved.

As with other anti-VEGF drug products administered by intravitreal injections, uncertainties remain on potential role of brolucizumab in systemic AE occurrence, especially arterial thromboembolic events, venous thromboembolic events, hypertension and non-ocular haemorrhage which are known risks of anti-VEGF drugs by IV route due to pharmacological plausibility. Similar rates were reported compared to aflibercept but due to low systemic exposure, the relationship is not confirmed.

4.8. Conclusions

The overall B/R of Brolucizumab 6 mg is positive.

CHMP assessment report
EMA/23630/2020 Page 124/125

5. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of visual impairment due to DME for Beovu; as a consequence, sections 4.1, 4.4, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 8.1 (DME) of the RMP has also been submitted.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

CHMP assessment report
EMA/23630/2020 Page 125/125